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(21) International Application Number: PCT/US00/00768 (22) International Filing Date: 13 January 2000 (13.01.00) (30) Priority Data: 60/115,878 13 January 1999 (13.01.99) US 09/257,265 25 February 1999 (25.02.99) US 09/425,229 22 October 1999 (22.10.99) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 60/115,878 (CIP) Filed on 13 January 1999 (13.01.99) US 09/257,265 (CIP) Filed on 25 February 1999 (25.02.99) US 09/425,229 (CIP) Filed on 22 October 1999 (22.10.99) (71) Applicant (for all designated States except US): BAYER CORPORATION [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): RIEDL, Bernd [DE/DE]; Von Der Goltz Strasse 7, D-42329 Wuppertal (DE). DU-		MAS, Jacques [FR/US]; 821 Beechwood Road, Orange, CT 06477 (US). KHIRE, Uday [IN/US]; 101 Tanglewood Drive, Hamden, CT 06518 (US). LOWINGER, Timothy, B. [CA/JP]; # 203, 5-7 Chitose-cho, Nishinomiya City, Hyogo 662-0046 (JP). SCOTT, William, J. [US/US]; 210 Saddle Hill Drive, Guilford, CT 06437 (US). SMITH, Roger, A. [CA/US]; 65 Winterhill Road, Madison, CT 06443 (US). WOOD, Jill, E. [US/US]; 72 Pickwick Road, Hamden, CT 06517 (US). MONAHAN, Mary-Katherine [US/US]; 134 Park Avenue, Hamden, CT 06517 (US). NATERO, Reina [US/US]; 113 Edgecomb Street, Hamden, CT 06518 (US). RENICK, Joel [US/US]; 11 Wall Street #4, Milford, CT 06460 (US). SIBLEY, Robert, N. [US/US]; 1187 Mt. Carmel Avenue, North Haven, CT 06473 (US). (74) Agents: TRAVERSO, Richard, J. et al.; Millen, White, Zelano & Branigan, P.C., Suite 1400, Arlington Courthouse Plaza 1, 2200 Clarendon Boulevard, Arlington, VA 22201 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: ω -CARBOXY ARYL SUBSTITUTED DIPHENYL UREAS AS p38 KINASE INHIBITORS (57) Abstract <p>This invention relates to the use of a group of aryl ureas in treating p38 mediated diseases, and pharmaceutical compositions for use in such therapy.</p>			

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**ω -CARBOXY ARYL SUBSTITUTED DIPHENYL UREAS AS
p38 KINASE INHIBITORS**

15

Cross-Reference to Related Applications

This is a continuation-in-part of Serial No. 09/257,265 filed February 25, 1999 and a continuation-in-part of Serial No. 60/115,878 filed January 13, 1999.

Field of the Invention

20 This invention relates to the use of a group of aryl ureas in treating cytokine mediated diseases and proteolytic enzyme mediated diseases, and pharmaceutical compositions for use in such therapy.

Background of the Invention

25 Two classes of effector molecules which are critical for the progression of rheumatoid arthritis are pro-inflammatory cytokines and tissue degrading proteases. Recently, a family of kinases was described which is instrumental in controlling the transcription and translation of the structural genes coding for these effector molecules.

30 The mitogen-activated protein (MAP) kinase family is made up of a series of structurally related proline-directed serine/threonine kinases which are activated either by growth factors (such as EGF) and phorbol esters (ERK), or by IL-1, TNF α or stress (p38, JNK). The MAP kinases are responsible for the activation of a wide variety of transcription factors and proteins involved in transcriptional control of

cytokine production. A pair of novel protein kinases involved in the regulation of cytokine synthesis was recently described by a group from SmithKline Beecham (Lee et al. *Nature* 1994, 372, 739). These enzymes were isolated based on their affinity to bond to a class of compounds, named CSAIDSs (cytokine suppressive anti-inflammatory drugs) by SKB. The CSAIDs, bicyclic pyridinyl imidazoles, have been shown to have cytokine inhibitory activity both *in vitro* and *in vivo*. The isolated enzymes, CSBP-1 and -2 (CSAID binding protein 1 and 2) have been cloned and expressed. A murine homologue for CSBP-2, p38, has also been reported (Han et al. *Science* 1994, 265, 808).

Early studies suggested that CSAIDs function by interfering with m-RNA translational events during cytokine biosynthesis. Inhibition of p38 has been shown to inhibit both cytokine production (eg., TNF α , IL-1, IL-6, IL-8) and proteolytic enzyme production (eg., MMP-1, MMP-3) *in vitro* and/or *in vivo*.

Clinical studies have linked TNF α production and/or signaling to a number of diseases including rheumatoid arthritis (Maini. *J. Royal Coll. Physicians London* 1996, 30, 344). In addition, excessive levels of TNF α have been implicated in a wide variety of inflammatory and/or immunomodulatory diseases, including acute rheumatic fever (Yegin et al. *Lancet* 1997, 349, 170), bone resorption (Pacifici et al. *J. Clin. Endocrinol. Metabol.* 1997, 82, 29), postmenopausal osteoporosis (Pacifici et al. *J. Bone Mineral Res.* 1996, 11, 1043), sepsis (Blackwell et al. *Br. J. Anaesth.* 1996, 77, 110), gram negative sepsis (Debets et al. *Prog. Clin. Biol. Res.* 1989, 308, 463), septic shock (Tracey et al. *Nature* 1987, 330, 662; Girardin et al. *New England J. Med.* 1988, 319, 397), endotoxic shock (Beutler et al. *Science* 1985, 229, 869; Ashkenasi et al. *Proc. Nat'l. Acad. Sci. USA* 1991, 88, 10535), toxic shock syndrome, (Saha et al. *J. Immunol.* 1996, 157, 3869; Lina et al. *FEMS Immunol. Med. Microbiol.* 1996, 13, 81), systemic inflammatory response syndrome (Anon. *Crit. Care Med.* 1992, 20, 864), inflammatory bowel diseases (Stokkers et al. *J. Inflamm.* 1995-6, 47, 97) including Crohn's disease (van Deventer et al. *Aliment. Pharmacol. Therapeu.* 1996, 10 (Suppl. 2), 107; van Dullemen et al. *Gastroenterology* 1995, 109, 129) and ulcerative colitis (Masuda et al. *J. Clin. Lab.*

Immunol. 1995, 46, 111), Jarisch-Herxheimer reactions (Fekade et al. *New England J. Med.* 1996, 335, 311), asthma (Amrani et al. *Rev. Malad. Respir.* 1996, 13, 539), adult respiratory distress syndrome (Roten et al. *Am. Rev. Respir. Dis.* 1991, 143, 590; Suter et al. *Am. Rev. Respir. Dis.* 1992, 145, 1016), acute pulmonary fibrotic diseases (Pan et al. *Pathol. Int.* 1996, 46, 91), pulmonary sarcoidosis (Ishioka et al. *Sarcoidosis Vasculitis Diffuse Lung Dis.* 1996, 13, 139), allergic respiratory diseases (Casale et al. *Am. J. Respir. Cell Mol. Biol.* 1996, 15, 35), silicosis (Gossart et al. *J. Immunol.* 1996, 156, 1540; Vanhee et al. *Eur. Respir. J.* 1995, 8, 834), coal worker's pneumoconiosis (Borm et al. *Am. Rev. Respir. Dis.* 1988, 138, 1589), alveolar injury (Horinouchi et al. *Am. J. Respir. Cell Mol. Biol.* 1996, 14, 1044), hepatic failure (Gantner et al. *J. Pharmacol. Exp. Therap.* 1997, 280, 53), liver disease during acute inflammation (Kim et al. *J. Biol. Chem.* 1997, 272, 1402), severe alcoholic hepatitis (Bird et al. *Ann. Intern. Med.* 1990, 112, 917), malaria (Grau et al. *Immunol. Rev.* 1989, 112, 49; Taverne et al. *Parasitol. Today* 1996, 12, 290) including *Plasmodium falciparum* malaria (Perlmann et al. *Infect. Immunit.* 1997, 65, 116) and cerebral malaria (Rudin et al. *Am. J. Pathol.* 1997, 150, 257), non-insulin-dependent diabetes mellitus (NIDDM; Stephens et al. *J. Biol. Chem.* 1997, 272, 971; Ofei et al. *Diabetes* 1996, 45, 881), congestive heart failure (Doyama et al. *Int. J. Cardiol.* 1996, 54, 217; McMurray et al. *Br. Heart J.* 1991, 66, 356), damage following heart disease (Malkiel et al. *Mol. Med. Today* 1996, 2, 336), atherosclerosis (Parums et al. *J. Pathol.* 1996, 179, A46), Alzheimer's disease (Fagarasan et al. *Brain Res.* 1996, 723, 231; Aisen et al. *Gerontology* 1997, 43, 143), acute encephalitis (Ichiyama et al. *J. Neurol.* 1996, 243, 457), brain injury (Cannon et al. *Crit. Care Med.* 1992, 20, 1414; Hansbrough et al. *Surg. Clin. N. Am.* 1987, 67, 69; Marano et al. *Surg. Gynecol. Obstetr.* 1990, 170, 32), multiple sclerosis (M.S.; Coyle. *Adv. Neuroimmunol.* 1996, 6, 143; Matusevicius et al. *J. Neuroimmunol.* 1996, 66, 115) including demyelination and oligodendrocyte loss in multiple sclerosis (Brosnan et al. *Brain Pathol.* 1996, 6, 243), advanced cancer (MucWierzgon et al. *J. Biol. Regulators Homeostatic Agents* 1996, 10, 25), lymphoid malignancies (Levy et al. *Crit. Rev. Immunol.* 1996, 16, 31), pancreatitis

(Exley et al. *Gut* 1992, 33, 1126) including systemic complications in acute pancreatitis (McKay et al. *Br. J. Surg.* 1996, 83, 919), impaired wound healing in infection inflammation and cancer (Buck et al. *Am. J. Pathol.* 1996, 149, 195), myelodysplastic syndromes (Raza et al. *Int. J. Hematol.* 1996, 63, 265), systemic lupus erythematosus (Maury et al. *Arthritis Rheum.* 1989, 32, 146), biliary cirrhosis (Miller et al. *Am. J. Gastroenterolog.* 1992, 87, 465), bowel necrosis (Sun et al. *J. Clin. Invest.* 1988, 81, 1328), psoriasis (Christophers. *Austr. J. Dermatol.* 1996, 37, S4), radiation injury (Redlich et al. *J. Immunol.* 1996, 157, 1705), and toxicity following administration of monoclonal antibodies such as OKT3 (Brod et al. *Neurology* 1996, 46, 1633). TNF α levels have also been related to host-versus-graft reactions (Piguet et al. *Immunol. Ser.* 1992, 56, 409) including ischemia reperfusion injury (Colletti et al. *J. Clin. Invest.* 1989, 85, 1333) and allograft rejections including those of the kidney (Maury et al. *J. Exp. Med.* 1987, 166, 1132), liver (Imagawa et al. *Transplantation* 1990, 50, 219), heart (Bolling et al. *Transplantation* 1992, 53, 283), and skin (Stevens et al. *Transplant. Proc.* 1990, 22, 1924), lung allograft rejection (Grossman et al. *Immunol. Allergy Clin. N. Am.* 1989, 9, 153) including chronic lung allograft rejection (obliterative bronchitis; LoCicero et al. *J. Thorac. Cardiovasc. Surg.* 1990, 99, 1059), as well as complications due to total hip replacement (Cirino et al. *Life Sci.* 1996, 59, 86). TNF α has also been linked to infectious diseases (review: Beutler et al. *Crit. Care Med.* 1993, 21, 5423; Degre. *Biotherapy* 1996, 8, 219) including tuberculosis (Rook et al. *Med. Malad. Infect.* 1996, 26, 904), *Helicobacter pylori* infection during peptic ulcer disease (Beales et al. *Gastroenterology* 1997, 112, 136), Chaga's disease resulting from *Trypanosoma cruzi* infection (Chandrasekar et al. *Biochem. Biophys. Res. Commun.* 1996, 223, 365), effects of Shiga-like toxin resulting from *E. coli* infection (Harel et al. *J. Clin. Invest.* 1992, 56, 40), the effects of enterotoxin A resulting from *Staphylococcus* infection (Fischer et al. *J. Immunol.* 1990, 144, 4663), meningococcal infection (Waage et al. *Lancet* 1987, 355; Ossege et al. *J. Neurolog. Sci.* 1996, 144, 1), and infections from *Borrelia burgdorferi* (Brandt et al. *Infect. Immunol.* 1990, 58, 983), *Treponema pallidum* (Chamberlin et

al. *Infect. Immunol.* 1989, 57, 2872), cytomegalovirus (CMV; Geist et al. *Am. J. Respir. Cell Mol. Biol.* 1997, 16, 31), influenza virus (Beutler et al. *Clin. Res.* 1986, 34, 491a), Sendai virus (Goldfield et al. *Proc. Nat'l. Acad. Sci. USA* 1989, 87, 1490), Theiler's encephalomyelitis virus (Sierra et al. *Immunology* 1993, 78, 399),
5 and the human immunodeficiency virus (HIV; Poli. *Proc. Nat'l. Acad. Sci. USA* 1990, 87, 782; Vyakarnam et al. *AIDS* 1990, 4, 21; Badley et al. *J. Exp. Med.* 1997, 185, 55).

Because inhibition of p38 leads to inhibition of TNF α production, p38 inhibitors will be useful in treatment of the above listed diseases.

10 A number of diseases are thought to be mediated by excess or undesired matrix-destroying metalloprotease (MMP) activity or by an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases (TIMPs). These include osteoarthritis (Woessner et al. *J. Biol. Chem.* 1984, 259, 3633), rheumatoid arthritis (Mullins et al. *Biochim. Biophys. Acta* 1983, 695, 117; Woolley et al. *Arthritis Rheum.* 1977, 20, 1231; Gravallesse et al. *Arthritis Rheum.* 1991, 34, 1076), septic
15 arthritis (Williams et al. *Arthritis Rheum.* 1990, 33, 533), tumor metastasis (Reich et al. *Cancer Res.* 1988, 48, 3307; Matrisian et al. *Proc. Nat'l. Acad. Sci., USA* 1986, 83, 9413), periodontal diseases (Overall et al. *J. Periodontal Res.* 1987, 22, 81), corneal ulceration (Burns et al. *Invest. Ophthalmol. Vis. Sci.* 1989, 30, 1569),
20 proteinuria (Baricos et al. *Biochem. J.* 1988, 254, 609), coronary thrombosis from atherosclerotic plaque rupture (Henney et al. *Proc. Nat'l. Acad. Sci., USA* 1991, 88, 8154), aneurysmal aortic disease (Vine et al. *Clin. Sci.* 1991, 81, 233), birth control (Woessner et al. *Steroids* 1989, 54, 491), dystrophic epidermolysis bullosa (Kronberger et al. *J. Invest. Dermatol.* 1982, 79, 208), degenerative cartilage loss
25 following traumatic joint injury, osteopenias mediated by MMP activity, temporo mandibular joint disease, and demyelating diseases of the nervous system (Chantry et al. *J. Neurochem.* 1988, 50, 688).

Because inhibition of p38 leads to inhibition of MMP production, p38 inhibitors will be useful in treatment of the above listed diseases.

Inhibitors of p38 are active in animal models of TNF α production, including a murine lipopolysaccharide (LPS) model of TNF α production. Inhibitors of p38 are active in a number of standard animal models of inflammatory diseases, including carrageenan-induced edema in the rat paw, arachadonic acid-induced edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced arthritis, and Freund's adjuvant-induced arthritis in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the above-mentioned cytokines and/or proteolytic enzymes.

The need for new therapies is especially important in the case of arthritic diseases. The primary disabling effect of osteoarthritis, rheumatoid arthritis and septic arthritis is the progressive loss of articular cartilage and thereby normal joint function. No marketed pharmaceutical agent is able to prevent or slow this cartilage loss, although nonsteroidal antiinflammatory drugs (NSAIDs) have been given to control pain and swelling. The end result of these diseases is total loss of joint function which is only treatable by joint replacement surgery. P38 inhibitors will halt or reverse the progression of cartilage loss and obviate or delay surgical intervention.

Several patents have appeared claiming polyarylimidazoles and/or compounds containing polyarylimidazoles as inhibitors of p38 (for example, Lee et al. WO 95/07922; Adams et al. WO 95/02591; Adams et al. WO 95/13067; Adams et al. WO 95/31451). It has been reported that arylimidazoles complex to the ferric form of cytochrome P450_{cam} (Harris et al. *Mol. Eng.* 1995, 5, 143, and references therein), causing concern that these compounds may display structure-related toxicity (Howard-Martin et al. *Toxicol. Pathol.* 1987, 15, 369). Therefore, there remains a need for improved p38 inhibitors.

Summary of the Invention

This invention provides compounds, generally described as aryl ureas, including both aryl and heteroaryl analogues, which inhibit p38 mediated events and

thus inhibit the production of cytokines (such as $\text{TNF}\alpha$, IL-1 and IL-8) and proteolytic enzymes (such as MMP-1 and MMP-3). The invention also provides a method of treating a cytokine mediated disease state in humans or mammals, wherein the cytokine is one whose production is affected by p38. Examples of such
5 cytokines include, but are not limited to $\text{TNF}\alpha$, IL-1 and IL-8. The invention also provides a method of treating a protease mediated disease state in humans or mammals, wherein the protease is one whose production is affected by p38. Examples of such proteases include, but are not limited to collagenase (MMP-1) and stromelysin (MMP-3).

10 Accordingly, these compounds are useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases as rheumatoid arthritis, osteoarthritis, septic arthritis, rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome,
15 inflammatory bowel diseases including Crohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic diseases, pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including
20 *Plasmodium falciparum* malaria and cerebral malaria, non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis including demyelination and oligodendrocyte loss in multiple sclerosis, advanced cancer, lymphoid malignancies, tumor metastasis, pancreatitis,
25 including systemic complications in acute pancreatitis, impaired wound healing in infection, inflammation and cancer, periodontal diseases, corneal ulceration, proteinuria, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury, toxicity following administration of monoclonal antibodies such as OKT3, host-versus-graft reactions
30 including ischemia reperfusion injury and allograft rejections including kidney,

liver, heart, and skin allograft rejections, lung allograft rejection including chronic lung allograft rejection (obliterative bronchitis) as well as complications due to total hip replacement, and infectious diseases including tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enterotoxin A resulting from *Staphylococcus* infection, meningococcal infection, and infections from *Borrelia burgdorferi*, *Treponema pallidum*, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

The present invention, therefore, provides compounds generally described as aryl ureas, including both aryl and heteroaryl analogues, which inhibit the p38 pathway. The invention also provides a method for treatment of p38-mediated disease states in humans or mammals, e.g., disease states mediated by one or more cytokines or proteolytic enzymes produced and/or activated by a p38 mediated process. Thus, the invention is directed to compounds, compositions and methods for the treatment of diseases mediated by p38 kinase wherein a compound of Formula I is administered or a pharmaceutically acceptable salt thereof.

A - D - B (I)

In formula I, D is -NH-C(O)-NH- ,

A is a substituted moiety of up to 40 carbon atoms of the formula: $\text{-L-(M-L}^1\text{)}_q$, where L is a 5 or 6 membered cyclic structure bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L^1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound

directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

5 R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by
10 halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

15 a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

20 $-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

25 b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen,

hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of CN, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of $-CN$, -

CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷, with R⁷ as defined above.

In formula I, suitable hetaryl groups include, but are not limited to, 5-12 carbon-atom aromatic rings or ring systems containing 1-3 rings, at least one of which is aromatic, in which one or more, e.g., 1-4 carbon atoms in one or more of the rings can be replaced by oxygen, nitrogen or sulfur atoms. Each ring typically has 3-7 atoms. For example, B can be 2- or 3-furyl, 2- or 3-thienyl, 2- or 4-triazinyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,3,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5- 6- or 7-benzisoxazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benz-1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinoliny, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinoliny, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, or 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, or additionally optionally substituted phenyl, 2- or 3-thienyl, 1,3,4-thiadiazolyl, 3-pyrrolyl, 3-pyrazolyl, 2-thiazolyl or 5-thiazolyl, etc. For example, B can be 4-methyl-phenyl, 5-methyl-2-thienyl, 4-methyl-2-thienyl, 1-methyl-3-pyrrolyl, 1-methyl-3-pyrazolyl, 5-methyl-2-thiazolyl or 5-methyl-1,2,4-thiadiazol-2-yl.

Suitable alkyl groups and alkyl portions of groups, e.g., alkoxy, etc. throughout include methyl, ethyl, propyl, butyl, etc., including all straight-chain and branched isomers such as isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, etc.

Suitable aryl groups which do not contain heteroatoms include, for example,
5 phenyl and 1- and 2-naphthyl.

The term "cycloalkyl", as used herein, refers to cyclic structures with or without alkyl substituents such that, for example, "C₄ cycloalkyl" includes methyl substituted cyclopropyl groups as well as cyclobutyl groups. The term "cycloalkyl", as used herein also includes saturated heterocyclic groups.

10 Suitable halogen groups include F, Cl, Br, and/or I, from one to per-substitution (i.e. all H atoms on a group replaced by a halogen atom) being possible where an alkyl group is substituted by halogen, mixed substitution of halogen atom types also being possible on a given moiety.

The invention also relates to compounds *per se*, of formula I.

15 The present invention is also directed to pharmaceutically acceptable salts of formula I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulphonic acid, *p*-toluenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic
20 acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li⁺ Na⁺ or
25 K⁺), alkaline earth cations (e.g., Mg⁺², Ca⁺² or Ba⁺²), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-

diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

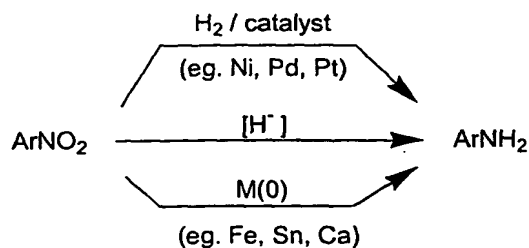
A number of the compounds of Formula I possess asymmetric carbons and can therefore exist in racemic and optically active forms. Methods of separation of enantiomeric and diastereomeric mixtures are well known to one skilled in the art. The present invention encompasses any isolated racemic or optically active form of compounds described in Formula I which possess p38 kinase inhibitory activity.

General Preparative Methods

The compounds of Formula I may be prepared by use of known chemical reactions and procedures, some from starting materials which are commercially available. Nevertheless, the following general preparative methods are presented to aid one of skill in the art in synthesizing these compounds, with more detailed particular examples being presented in the experimental section describing the working examples.

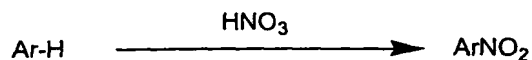
Substituted anilines may be generated using standard methods (March. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York (1985). Larock. *Comprehensive Organic Transformations*; VCH Publishers: New York (1989)). As shown in Scheme I, aryl amines are commonly synthesized by reduction of nitroaryls using a metal catalyst, such as Ni, Pd, or Pt, and H₂ or a hydride transfer agent, such as formate, cyclohexadiene, or a borohydride (Rylander. *Hydrogenation Methods*; Academic Press: London, UK (1985)). Nitroaryls may also be directly reduced using a strong hydride source, such as LiAlH₄ (Seyden-Penne. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH Publishers: New York (1991)), or using a zero valent metal, such as Fe, Sn or Ca, often in acidic media. Many methods exist for the synthesis of nitroaryls (March. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York (1985). Larock. *Comprehensive Organic Transformations*; VCH Publishers: New York (1989)).

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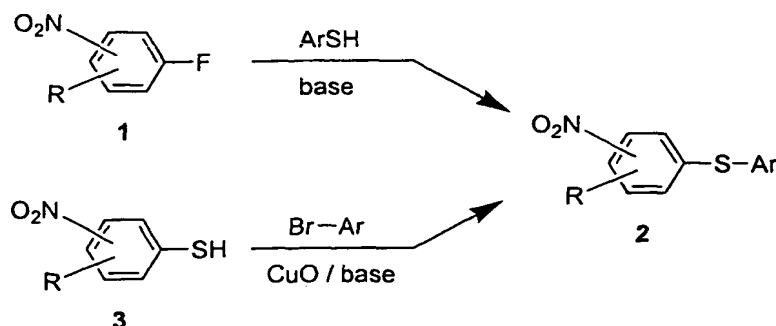
Scheme I Reduction of Nitroaryls to Aryl Amines

Nitroaryls are commonly formed by electrophilic aromatic nitration using HNO₃, or an alternative NO₂⁺ source. Nitroaryls may be further elaborated prior to reduction. Thus, nitroaryls substituted with



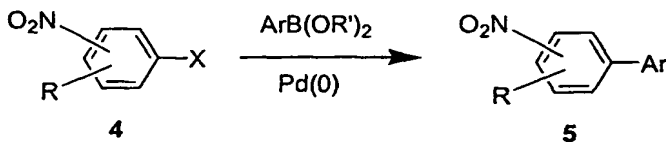
potential leaving groups (eg. F, Cl, Br, etc.) may undergo substitution reactions on treatment with nucleophiles, such as thiolate (exemplified in Scheme II) or

phenoxide. Nitroaryls may also undergo Ullman-type coupling reactions (Scheme II).



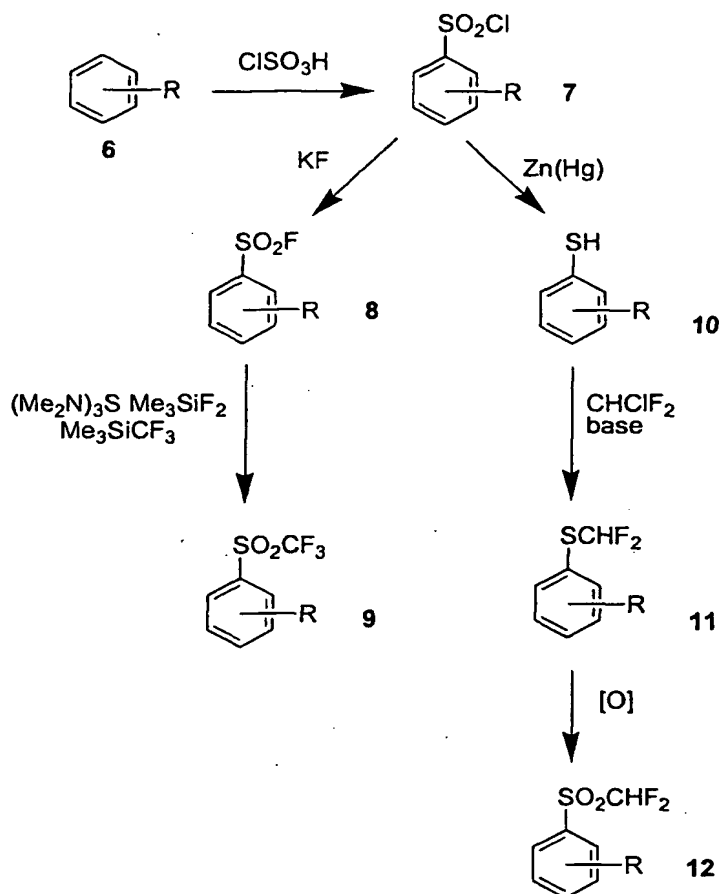
Scheme II Selected Nucleophilic Aromatic Substitution using Nitroaryls

Nitroaryls may also undergo transition metal mediated cross coupling reactions. For example, nitroaryl electrophiles, such as nitroaryl bromides, iodides or triflates, undergo palladium mediated cross coupling reactions with aryl nucleophiles, such as arylboronic acids (Suzuki reactions, exemplified below), aryltins (Stille reactions) or arylzincs (Negishi reaction) to afford the biaryl (5).



Either nitroaryls or anilines may be converted into the corresponding arenesulfonyl chloride (7) on treatment with chlorosulfonic acid. Reaction of the sulfonyl chloride with a fluoride source, such as KF then affords sulfonyl fluoride (8). Reaction of sulfonyl fluoride 8 with trimethylsilyl trifluoromethane in the presence of a fluoride source, such as tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) leads to the corresponding trifluoromethylsulfone (9). Alternatively, sulfonyl chloride 7 may be reduced to the

arenethiol (10), for example with zinc amalgum. Reaction of thiol 10 with CHClF_2 in the presence of base gives the difluoromethyl mercaptam (11), which may be oxidized to the sulfone (12) with any of a variety of oxidants, including CrO_3 -acetic anhydride (Sedova et al. *Zh. Org. Khim.* 1970, 6, 568).

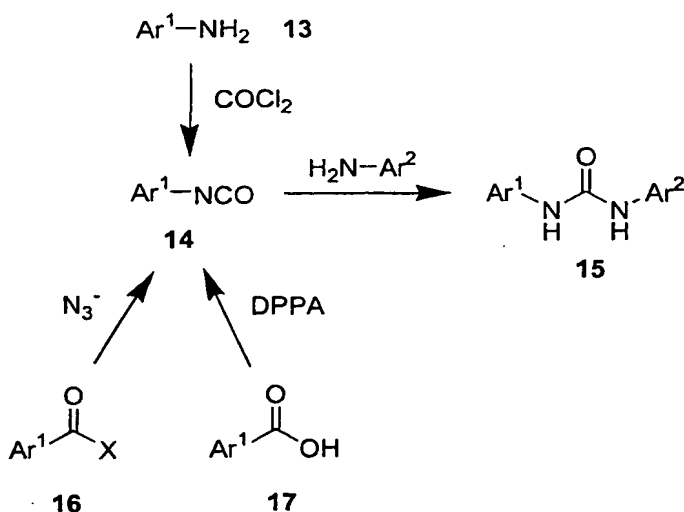


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Scheme III Selected Methods of Fluorinated Aryl Sulfone Synthesis

As shown in Scheme IV, non-symmetrical urea formation may involve reaction of an aryl isocyanate (14) with an aryl amine (13). The heteroaryl isocyanate may be synthesized from a heteroaryl amine by treatment with phosgene or a phosgene equivalent, such as trichloromethyl chloroformate (diphosgene), bis(trichloromethyl) carbonate (triphosgene), or N,N' -carbonyldiimidazole (CDI).

The isocyanate may also be derived from a heterocyclic carboxylic acid derivative, such as an ester, an acid halide or an anhydride by a Curtius-type rearrangement. Thus, reaction of acid derivative 16 with an azide source, followed by rearrangement affords the isocyanate. The corresponding carboxylic acid (17) may also be subjected to Curtius-type rearrangements using diphenylphosphoryl azide (DPPA) or a similar reagent.



Scheme IV Selected Methods of Non-Symmetrical Urea Formation

Finally, ureas may be further manipulated using methods familiar to those skilled in the art.

The invention also includes pharmaceutical compositions including a compound of Formula I, and a physiologically acceptable carrier.

The compounds may be administered orally, topically, parenterally, by inhalation or spray, vaginally, rectally or sublingually in dosage unit formulations.

The term 'administration by injection' includes intravenous, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. Dermal administration may include topical application or transdermal administration. One or more compounds may be present in association with one or

more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene

stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide
5 with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

10 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening,
15 flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening
20 agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Compounds of the invention may also be administrated transdermally using
25 methods known to those skilled in the art (see, for example: Chien; "Transdermal Controlled Systemic Medications"; Marcel Dekker, Inc.; 1987. Lipp et al. WO94/04157 3Mar94). For example, a solution or suspension of a compound of Formula I in a suitable volatile solvent optionally containing penetration enhancing agents can be combined with additional additives known to those skilled in the art,
30 such as matrix materials and bacteriocides. After sterilization, the resulting mixture

can be formulated following known procedures into dosage forms. In addition, on treatment with emulsifying agents and water, a solution or suspension of a compound of Formula I may be formulated into a lotion or salve.

Suitable solvents for processing transdermal delivery systems are known to those skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol, lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate, polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform, trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include mixtures of one or more materials selected from lower alcohols, lower ketones, lower carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

Suitable penetration enhancing materials for transdermal delivery system are known to those skilled in the art, and include, for example, monohydroxy or polyhydroxy alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated C₈-C₁₈ fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated C₈-C₁₈ fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to 24 carbons such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl isobutyl tertbutyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristinic acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate, diisopropyl sebacate, diisopropyl maleate, or diisopropyl fumarate. Additional penetration enhancing materials include phosphatidyl derivatives such as lecithin or cephalin, terpenes, amides, ketones, ureas and their derivatives, and ethers such as dimethyl isosorbide and diethyleneglycol monoethyl ether. Suitable penetration enhancing formulations may also include mixtures of one or more materials selected from monohydroxy or polyhydroxy alcohols, saturated or unsaturated C₈-C₁₈ fatty alcohols, saturated or unsaturated C₈-C₁₈ fatty acids, saturated or unsaturated fatty esters with up to 24 carbons, diesters of saturated or unsaturated dicarboxylic acids with a total of up to

24 carbons, phosphatidyl derivatives, terpenes, amides, ketones, ureas and their derivatives, and ethers.

Suitable binding materials for transdermal delivery systems are known to those skilled in the art and include polyacrylates, silicones, polyurethanes, block
5 polymers, styrenebutadiene copolymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylenes, and silicates may also be used as matrix components. Additional additives, such as viscous resins or oils may be added to increase the viscosity of the matrix.

Pharmaceutical compositions of the invention may also be in the form of oil-
10 in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides,
15 for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain
20 a demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal or vaginal temperature and will therefore melt
25 in the rectum or vagina to release the drug. Such materials include cocoa butter and polyethylene glycols.

For all regimens of use disclosed herein for compounds of Formula I, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily dosage for administration by injection, including intravenous,
30 intramuscular, subcutaneous and parenteral injections, and use of infusion

techniques will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The transdermal concentration will preferably be that
5 required to maintain a daily dose of from 0.01 to 200 mg/Kg. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The daily inhalation dosage regimen will preferably be from 0.01 to 10 mg/Kg of total body weight.

10 It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for a given patient depends on a variety of factors, including specific activity of the compound administered, the age of the patient, the body
15 weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combination, and the severity of the condition undergoing therapy, etc. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of Formula
20 I or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment tests.

The compounds of Figure I are producible from known compounds (or from starting
25 materials which, in turn, are producible from known compounds), e.g., through the general preparative methods shown above. The activity of a given compound to inhibit raf kinase can be routinely assayed, e.g., according to procedures disclosed below. The following examples are for illustrative purposes only and are not intended, nor should they be construed to limit the invention in any way.

30

The entire disclosure of all applications, patents and publications cited above and below are hereby incorporated by reference, including non-provisional application Serial No. 09/257,265 filed February 25, 1999 and provisional application serial number 60/115,878, filed on January 13, 1999.

5

The following examples are for illustrative purposes only and are not intended, nor should they be construed to limit the invention in any way.

EXAMPLES

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of dry argon or dry nitrogen, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Unless otherwise stated, the term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mmHg. Unless otherwise stated, the term 'under high vacuum' refers to a vacuum of 0.4 – 1.0 mmHg.

All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by weight.

Commercial grade reagents and solvents were used without further purification. *N*-cyclohexyl-*N'*-(methylpolystyrene)carbodiimide was purchased from Calbiochem-Novabiochem Corp. 3-*tert*-Butylaniline, 5-*tert*-butyl-2-methoxyaniline, 4-bromo-3-(trifluoromethyl)aniline, 4-chloro-3-(trifluoromethyl)aniline 2-methoxy-5-(trifluoromethyl)aniline, 4-*tert*-butyl-2-nitroaniline, 3-amino-2-naphthol, ethyl 4-isocyanatobenzoate, *N*-acetyl-4-chloro-2-methoxy-5-(trifluoromethyl)aniline and 4-chloro-3-(trifluoromethyl)phenyl isocyanate were purchased and used without further purification. Syntheses of 3-amino-2-methoxyquinoline (E. Cho et al. WO 98/00402; A. Cordi et al. EP 542,609; *IBID Bioorg. Med. Chem.* 3, 1995, 129), 4-(3-carbamoylphenoxy)-1-nitrobenzene (K. Ikawa *Yakugaku Zasshi* 79, 1959, 760; *Chem. Abstr.* 53, 1959, 12761b), 3-*tert*-butylphenyl isocyanate (O. Rohr et al. DE

2,436,108) and 2-methoxy-5-(trifluoromethyl)phenyl isocyanate (K. Inukai et al. JP 42,025,067; *IBID Kogyo Kagaku Zasshi* 70, 1967, 491) have previously been described.

- 5 Thin-layer chromatography (TLC) was performed using Whatman® pre-coated glass-backed silica gel 60A F-254 250 μ m plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, (d) immersion of the plate in
10 a cerium sulfate solution followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of 2,4-dinitrophenylhydrazine followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.
- 15 Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier transform infrared spectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (^1H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer
20 with either Me_4Si (δ 0.00) or residual protonated solvent (CHCl_3 δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (^{13}C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent (CDCl_3 δ 77.0; MeOD-d_3 ; δ 49.0; DMSO-d_6 δ 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were either obtained as electron
25 impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) were obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Vacumetrics Desorption Chemical Ionization Probe for sample introduction. The ion source was maintained at 250 °C. Electron impact ionization was performed with electron energy of 70 eV and a trap current of
30 300 μA . Liquid-caesium secondary ion mass spectra (FAB-MS), an updated version

of fast atom bombardment were obtained using a Kratos Concept 1-H spectrometer. Chemical ionization mass spectra (CI-MS) were obtained using a Hewlett Packard MS-Engine (5989A) with methane or ammonia as the reagent gas (1×10^{-4} torr to 2.5×10^{-4} torr). The direct insertion desorption chemical ionization (DCI) probe
5 (Vaccumetrics, Inc.) was ramped from 0-1.5 amps in 10 sec and held at 10 amps until all traces of the sample disappeared (~1-2 min). Spectra were scanned from 50-800 amu at 2 sec per scan. HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a C-18 column, and a Finnigan LCQ ion trap
10 mass spectrometer with electrospray ionization. Spectra were scanned from 120-800 amu using a variable ion time according to the number of ions in the source. Gas chromatography - ion selective mass spectra (GC-MS) were obtained with a Hewlett Packard 5890 gas chromatograph equipped with an HP-1 methyl silicone column (0.33 mM coating; 25 m x 0.2 mm) and a Hewlett Packard 5971 Mass
15 Selective Detector (ionization energy 70 eV). Elemental analyses are conducted by Robertson Microlit Labs, Madison NJ.

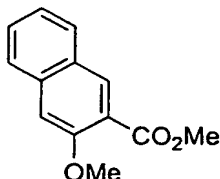
All compounds displayed NMR spectra, LRMS and either elemental analysis or HRMS consistent with assigned structures.

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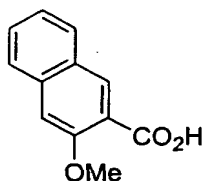
List of Abbreviations and Acronyms:

AcOH	acetic acid
anh	anhydrous
atm	atmosphere(s)
25 BOC	<i>tert</i> -butoxycarbonyl
CDI	1,1'-carbonyl diimidazole
conc	concentrated
d	day(s)
dec	decomposition
30 DMAC	<i>N,N</i> -dimethylacetamide

	DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethylsulfoxide
	DPPA	diphenylphosphoryl azide
5	EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
	EtOAc	ethyl acetate
	EtOH	ethanol (100%)
	Et ₂ O	diethyl ether
	Et ₃ N	triethylamine
10	h	hour(s)
	HOBt	1-hydroxybenzotriazole
	<i>m</i> -CPBA	3-chloroperoxybenzoic acid
	MeOH	methanol
	pet. ether	petroleum ether (boiling range 30-60 °C)
15	temp.	temperature
	THF	tetrahydrofuran
	TFA	trifluoroAcOH
	Tf	trifluoromethanesulfonyl

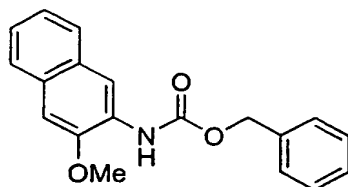
A. General Methods for Synthesis of Substituted Anilines**A1. General Method for Aryl Amine Formation via Ether Formation Followed by Ester Saponification, Curtius Rearrangement, and Carbamate Deprotection. Synthesis of 2-Amino-3-methoxynaphthalene.****Step 1. Methyl 3-methoxy-2-naphthoate**

A slurry of methyl 3-hydroxy-2-naphthoate (10.1 g, 50.1 mmol) and K_2CO_3 (7.96 g, 57.6 mmol) in DMF (200 mL) was stirred at room temp. for 15 min., then treated with iodomethane (3.43 mL, 55.1 mmol). The mixture was allowed to stir at room temp. overnight, then was treated with water (200 mL). The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with a saturated NaCl solution (100 mL), dried ($MgSO_4$), concentrated under reduced pressure (approximately 0.4 mmHg overnight) to give methyl 3-methoxy-2-naphthoate as an amber oil (10.30 g): 1H -NMR ($DMSO-d_6$) δ 2.70 (s, 3H), 2.85 (s, 3H), 7.38 (app t, $J=8.09$ Hz, 1H), 7.44 (s, 1H), 7.53 (app t, $J=8.09$ Hz, 1H), 7.84 (d, $J=8.09$ Hz, 1H), 7.90 (s, 1H), 8.21 (s, 1H).

**Step 2. 3-Methoxy-2-naphthoic acid**

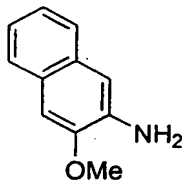
A solution of methyl 3-methoxy-2-naphthoate (6.28 g, 29.10 mmol) and water (10 mL) in MeOH (100 mL) at room temp. was treated with a 1 N NaOH solution (33.4 mL, 33.4 mmol). The mixture was heated at the reflux temp. for 3 h, cooled to room temp., and made acidic with a 10% citric acid solution. The resulting solution was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed

with a saturated NaCl solution, dried (MgSO_4) and concentrated under reduced pressure. The residue was triturated with hexane then washed several times with hexane to give 3-methoxy-2-naphthoic acid as a white solid (5.40 g, 92%): $^1\text{H-NMR}$ (DMSO- d_6) δ 3.88 (s, 3H), 7.34-7.41 (m, 2H), 7.49-7.54 (m, 1H), 7.83 (d, $J=8.09$ Hz, 1H), 7.91 (d, $J=8.09$ Hz, 1H), 8.19 (s, 1H), 12.83 (br s, 1H).



Step 3. 2-(N-(Carbobenzyloxy)amino)-3-methoxynaphthalene

A solution of 3-methoxy-2-naphthoic acid (3.36 g, 16.6 mmol) and Et_3N (2.59 mL, 18.6 mmol) in anhydrous toluene (70 mL) was stirred at room temp. for 15 min., then treated with a solution of DPPA (5.12 g, 18.6 mmol) in toluene (10 mL) *via* pipette. The resulting mixture was heated at 80 °C for 2 h. After cooling the mixture to room temp., benzyl alcohol (2.06 mL, 20 mmol) was added *via* syringe. The mixture was then warmed to 80 °C overnight. The resulting mixture was cooled to room temp., quenched with a 10% citric acid solution, and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with a saturated NaCl solution, dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (14% EtOAc/86% hexane) to give 2-(N-(carbobenzyloxy)amino)-3-methoxynaphthalene as a pale yellow oil (5.1 g, 100%): $^1\text{H-NMR}$ (DMSO- d_6) δ 3.89 (s, 3H), 5.17 (s, 2H), 7.27-7.44 (m, 8H), 7.72-7.75 (m, 2H), 8.20 (s, 1H), 8.76 (s, 1H).

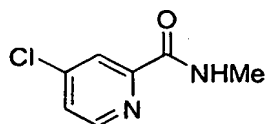


Step 4. 2-Amino-3-methoxynaphthalene

A slurry of 2-(N-(carbobenzyloxy)amino)-3-methoxynaphthalene (5.0 g, 16.3 mmol) and 10% Pd/C (0.5 g) in EtOAc (70 mL) was maintained under a H_2 atm (balloon)

at room temp. overnight. The resulting mixture was filtered through Celite® and concentrated under reduced pressure to give 2-amino-3-methoxynaphthalene as a pale pink powder (2.40 g, 85%): ¹H-NMR (DMSO-d₆) δ 3.86 (s, 3H), 6.86 (s, 2H), 7.04-7.16 (m, 2H), 7.43 (d, *J*=8.0 Hz, 1H), 7.56 (d, *J*=8.0 Hz, 1H); EI-MS *m/z* 173 (M⁺).

A2. Synthesis of ω-Carbamyl Anilines via Formation of a Carbamylpyridine Followed by Nucleophilic Coupling with an Aryl Amine. Synthesis of 4-(2-*N*-Methylcarbamyl-4-pyridyloxy)aniline

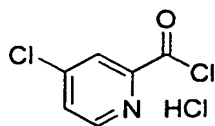


Step 1a. Synthesis of 4-chloro-*N*-methyl-2-pyridinecarboxamide via the Menisci reaction

Caution: this is a highly hazardous, potentially explosive reaction. To a stirring solution of 4-chloropyridine (10.0 g) in *N*-methylformamide (250 mL) at room temp. was added conc. H₂SO₄ (3.55 mL) to generate an exotherm. To this mixture was added H₂O₂ (30% wt in H₂O, 17 mL) followed by FeSO₄•7H₂O (0.56 g) to generate another exotherm. The resulting mixture was stirred in the dark at room temp. for 1 h, then warmed slowly over 4 h to 45 °C. When bubbling had subsided, the reaction was heated at 60 °C for 16 h. The resulting opaque brown solution was diluted with H₂O (700 mL) followed by a 10% NaOH solution (250 mL). The resulting mixture was extracted with EtOAc (3 x 500 mL). The organic phases were washed separately with a saturated NaCl solution (3 x 150 mL), then they were combined, dried (MgSO₄) and filtered through a pad of silica gel with the aid of EtOAc. The resulting brown oil was purified by column chromatography (gradient from 50% EtOAc/50% hexane to 80% EtOAc/20% hexane). The resulting yellow

oil crystallized at 0 °C over 72 h to give 4-chloro-*N*-methyl-2-pyridinecarboxamide (0.61 g, 5.3%): TLC (50% EtOAc/50% hexane) R_f 0.50; ^1H NMR (CDCl_3) δ 3.04 (d, $J=5.1$ Hz, 3H), 7.43 (dd, $J=5.4, 2.4$ Hz, 1H), 7.96 (br s, 1H), 8.21 (s, 1H), 8.44 (d, $J=5.1$ Hz, 1H); CI-MS m/z 171 ($(\text{M}+\text{H})^+$).

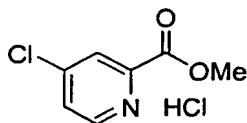
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Step 1b. Synthesis of 4-chloropyridine-2-carbonyl chloride HCl salt via picolinic acid

Anhydrous DMF (6.0 mL) was slowly added to SOCl_2 (180 mL) between 40° and 50 °C. The solution was stirred in that temperature range for 10 min. then picolinic acid (60.0 g, 487 mmol) was added in portions over 30 min. The resulting solution was heated at 72 °C (vigorous SO_2 evolution) for 16 h to generate a yellow solid precipitate. The resulting mixture was cooled to room temp., diluted with toluene (500 mL) and concentrated to 200 mL. The toluene addition/concentration process was repeated twice. The resulting nearly dry residue was filtered and the solids were washed with toluene (2 x 200 mL) and dried under high vacuum for 4 h to afford 4-chloropyridine-2-carbonyl chloride HCl salt as a yellow-orange solid (92.0 g, 89%).

15



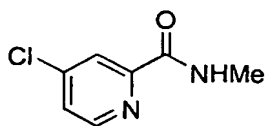
Step 2. Synthesis of methyl 4-chloropyridine-2-carboxylate HCl salt

Anh DMF (10.0 mL) was slowly added to SOCl_2 (300 mL) at 40-48 °C. The solution was stirred at that temp. range for 10 min., then picolinic acid (100 g, 812 mmol) was added over 30 min. The resulting solution was heated at 72 °C (vigorous SO_2 evolution) for 16 h to generate a yellow solid. The resulting mixture was cooled to room temp., diluted with toluene (500 mL) and concentrated to 200 mL. The toluene addition/concentration process was repeated twice. The resulting nearly dry residue was filtered, and the solids were washed with toluene (50 mL)

25

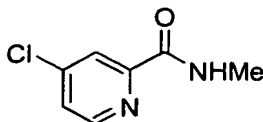
and dried under high vacuum for 4 hours to afford 4-chloropyridine-2-carbonyl chloride HCl salt as an off-white solid (27.2 g, 16%). This material was set aside.

5 The red filtrate was added to MeOH (200 mL) at a rate which kept the internal temperature below 55 °C. The contents were stirred at room temp. for 45 min., cooled to 5 °C and treated with Et₂O (200 mL) dropwise. The resulting solids were filtered, washed with Et₂O (200 mL) and dried under reduced pressure at 35 °C to provide methyl 4-chloropyridine-2-carboxylate HCl salt as a white solid (110 g, 65%): mp 108-112 °C; ¹H-NMR (DMSO-d₆) δ 3.88 (s, 3H); 7.82 (dd, *J*=5.5, 2.2 Hz, 1H); 8.08 (d, *J*=2.2 Hz, 1H); 8.68 (d, *J*=5.5 Hz, 1H); 10.68 (br s, 1H); HPLC ES-MS *m/z* 172 ((M+H)⁺).



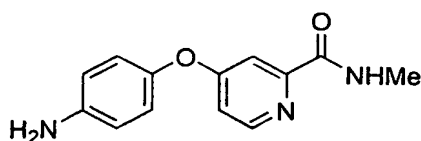
15 **Step 3a. Synthesis of 4-chloro-*N*-methyl-2-pyridinecarboxamide from methyl 4-chloropyridine-2-carboxylate**

A suspension of methyl 4-chloropyridine-2-carboxylate HCl salt (89.0 g, 428 mmol) in MeOH (75 mL) at 0 °C was treated with a 2.0 M methylamine solution in THF (1 L) at a rate which kept the internal temp. below 5 °C. The resulting mixture was stored at 3 °C for 5 h, then concentrated under reduced pressure. The resulting solids were suspended in EtOAc (1 L) and filtered. The filtrate was washed with a saturated NaCl solution (500 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford 4-chloro-*N*-methyl-2-pyridinecarboxamide as pale-yellow crystals (71.2 g, 97%): mp 41-43 °C; ¹H-NMR (DMSO-d₆) δ 2.81 (s, 3H), 7.74 (dd, *J*=5.1, 2.2 Hz, 1H), 8.00 (d, *J*=2.2, 1H), 8.61 (d, *J*=5.1 Hz, 1H), 8.85 (br d, 1H); CI-MS *m/z* 171 ((M+H)⁺).



Step 3b. Synthesis of 4-chloro-*N*-methyl-2-pyridinecarboxamide from 4-chloropyridine-2-carbonyl chloride

4-Chloropyridine-2-carbonyl chloride HCl salt (7.0 g, 32.95 mmol) was added in portions to a mixture of a 2.0 M methylamine solution in THF (100 mL) and MeOH (20 mL) at 0 °C. The resulting mixture was stored at 3 °C for 4 h, then concentrated under reduced pressure. The resulting nearly dry solids were suspended in EtOAc (100 mL) and filtered. The filtrate was washed with a saturated NaCl solution (2 x 100 mL), dried (Na₂SO₄) and concentrated under reduced pressure to provide 4-chloro-*N*-methyl-2-pyridinecarboxamide as a yellow, crystalline solid (4.95 g, 88%): mp 37-40 °C.

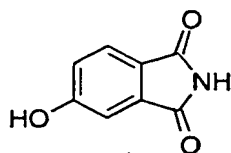


Step 4. Synthesis of 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline

A solution of 4-aminophenol (9.60 g, 88.0 mmol) in anh. DMF (150 mL) was treated with potassium *tert*-butoxide (10.29 g, 91.7 mmol), and the reddish-brown mixture was stirred at room temp. for 2 h. The contents were treated with 4-chloro-*N*-methyl-2-pyridinecarboxamide (15.0 g, 87.9 mmol) and K₂CO₃ (6.50 g, 47.0 mmol) and then heated at 80 °C for 8 h. The mixture was cooled to room temp. and separated between EtOAc (500 mL) and a saturated NaCl solution (500 mL). The aqueous phase was back-extracted with EtOAc (300 mL). The combined organic layers were washed with a saturated NaCl solution (4 x 1000 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The resulting solids were dried under reduced pressure at 35 °C for 3 h to afford 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline as a light-brown solid 17.9 g, 84%): ¹H-NMR (DMSO-*d*₆) δ 2.77 (d, *J*=4.8 Hz, 3H), 5.17 (br s, 2H), 6.64, 6.86 (AA'BB' quartet, *J*=8.4 Hz, 4H), 7.06 (dd, *J*=5.5, 2.5 Hz, 1H), 7.33 (d, *J*=2.5 Hz, 1H), 8.44 (d, *J*=5.5 Hz, 1H), 8.73 (br d, 1H); HPLC ES-MS *m/z* 244 ((*M*+*H*)⁺).

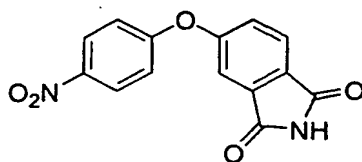
A3. General Method for the Synthesis of Anilines by Nucleophilic

Aromatic Addition Followed by Nitroarene Reduction. Synthesis of 5-(4-Aminophenoxy)isoindoline-1,3-dione



5 Step 1. Synthesis of 5-hydroxyisoindoline-1,3-dione

To a mixture of ammonium carbonate (5.28 g, 54.9 mmol) in conc. AcOH (25 mL) was slowly added 4-hydroxyphthalic acid (5.0 g, 27.45 mmol). The resulting mixture was heated at 120 °C for 45 min., then the clear, bright yellow mixture was heated at 160 °C for 2 h. The resulting mixture was maintained at 160 °C and was concentrated to approximately 15 mL, then was cooled to room temp. and adjusted pH 10 with a 1N NaOH solution. This mixture was cooled to 0 °C and slowly acidified to pH 5 using a 1N HCl solution. The resultant precipitate was collected by filtration and dried under reduced pressure to yield 5-hydroxyisoindoline-1,3-dione as a pale yellow powder as product (3.24 g, 72%): ¹H NMR (DMSO-d₆) δ 7.00-7.03 (m, 2H), 7.56 (d, *J*=9.3Hz, 1H).

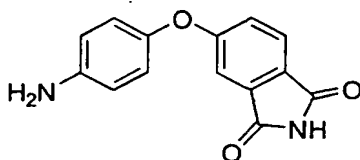


Step 2. Synthesis of 5-(4-nitrophenoxy)isoindoline-1,3-dione

To a stirring slurry of NaH (1.1 g, 44.9 mmol) in DMF (40 mL) at 0 °C was added a solution of 5-hydroxyisoindoline-1,3-dione (3.2 g, 19.6 mmol) in DMF (40 mL) dropwise. The bright yellow-green mixture was allowed to return to room temp. and was stirred for 1 h, then 1-fluoro-4-nitrobenzene (2.67 g, 18.7 mmol) was added via syringe in 3-4 portions. The resulting mixture was heated at 70 °C overnight, then cooled to room temp. and diluted slowly with water (150 mL), and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (MgSO₄) and

concentrated under reduced pressure to give 5-(4-nitrophenoxy)isoindoline-1,3-dione as a yellow solid (3.3 g, 62%): TLC (30% EtOAc/70% hexane) R_f 0.28; ^1H NMR (DMSO- d_6) δ 7.32 (d, $J=12$ Hz, 2H), 7.52-7.57 (m, 2H), 7.89 (d, $J=7.8$ Hz, 1H), 8.29 (d, $J=9$ Hz, 2H), 11.43 (br s, 1H); CI-MS m/z 285 ($(\text{M}+\text{H})^+$, 100%).

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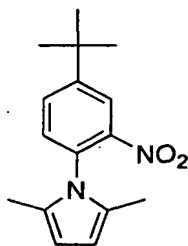


Step 3. Synthesis of 5-(4-aminophenoxy)isoindoline-1,3-dione

A solution of 5-(4-nitrophenoxy)isoindoline-1,3-dione (0.6 g, 2.11 mmol) in conc. AcOH (12 mL) and water (0.1 mL) was stirred under stream of argon while iron powder (0.59 g, 55.9 mmol) was added slowly. This mixture stirred at room temp. for 72 h, then was diluted with water (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (MgSO_4) and concentrated under reduced pressure to give 5-(4-aminophenoxy)isoindoline-1,3-dione as a brownish solid (0.4 g, 75%): TLC (50% EtOAc/50% hexane) R_f 0.27; ^1H NMR (DMSO- d_6) δ 5.14 (br s, 2H), 6.62 (d, $J=8.7$ Hz, 2H), 6.84 (d, $J=8.7$ Hz, 2H), 7.03 (d, $J=2.1$ Hz, 1H), 7.23 (dd, 1H), 7.75 (d, $J=8.4$ Hz, 1H), 11.02 (s, 1H); HPLC ES-MS m/z 255 ($(\text{M}+\text{H})^+$, 100%).

A4. General Method for the Synthesis of Pyrrolylanilines. Synthesis of 5-*tert*-Butyl-2-(2,5-dimethylpyrrolyl)aniline

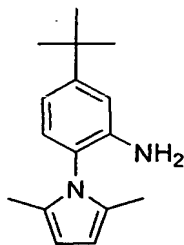
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Step 1. Synthesis of 1-(4-*tert*-butyl-2-nitrophenyl)-2,5-dimethylpyrrole

To a stirring solution of 2-nitro-4-*tert*-butylaniline (0.5 g, 2.57 mmol) in cyclohexane (10 mL) was added AcOH (0.1 mL) and acetonylacetone (0.299 g, 2.63

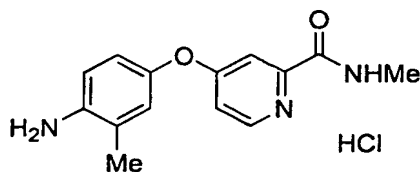
mmol) via syringe. The reaction mixture was heated at 120 °C for 72 h with azeotropic removal of volatiles. The reaction mixture was cooled to room temp., diluted with CH₂Cl₂ (10 mL) and sequentially washed with a 1N HCl solution (15 mL), a 1N NaOH solution (15 mL) and a saturated NaCl solution (15mL), dried (5 MgSO₄) and concentrated under reduced pressure. The resulting orange-brown solids were purified via column chromatography (60 g SiO₂; gradient from 6% EtOAc/94% hexane to 25% EtOAc/75% hexane) to give 1-(4-*tert*-butyl-2-nitrophenyl)-2,5-dimethylpyrrole as an orange-yellow solid (0.34 g, 49%): TLC (15% EtOAc/85% hexane) R_f 0.67; ¹H NMR (CDCl₃) δ 1.34 (s, 9H), 1.89 (s, 6H), 10 5.84 (s, 2H), 7.19-7.24 (m, 1H), 7.62 (dd, 1H), 7.88 (d, *J*=2.4 Hz, 1H); CI-MS *m/z* 273 ((M+H)⁺, 50%).



Step 2. Synthesis of 5-*tert*-Butyl-2-(2,5-dimethylpyrrolyl)aniline

A slurry of 1-(4-*tert*-butyl-2-nitrophenyl)-2,5-dimethylpyrrole (0.341 g, 1.25 mmol),
 5 10%Pd/C (0.056 g) and EtOAc (50 mL) under an H₂ atmosphere (balloon) was
 stirred for 72 h, then filtered through a pad of Celite®. The filtrate was concentrated
 under reduced pressure to give 5-*tert*-butyl-2-(2,5-dimethylpyrrolyl)aniline as
 yellowish solids (0.30 g, 99%): TLC (10% EtOAc/90% hexane) R_f 0.43; ¹H NMR
 (CDCl₃) δ 1.28 (s, 9H), 1.87-1.91 (m, 8H), 5.85 (br s, 2H), 6.73-6.96 (m, 3H), 7.28
 10 (br s, 1H).

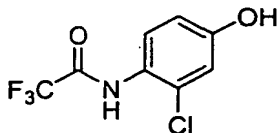
**A5. General Method for the Synthesis of Anilines from Anilines by
 Nucleophilic Aromatic Substitution. Synthesis of 4-(2-(*N*-
 Methylcarbamoyl)-4-pyridyloxy)-2-methylaniline HCl Salt**



15 A solution of 4-amino-3-methylphenol (5.45 g, 44.25 mmol) in dry
 dimethylacetamide (75 mL) was treated with potassium *tert*-butoxide (10.86 g,
 96.77 mmol) and the black mixture was stirred at room temp. until the flask had
 reached room temp. The contents were then treated with 4-chloro-*N*-methyl-2-
 20 pyridinecarboxamide (Method A2, Step 3b; 7.52 g, 44.2 mmol) and heated at 110
 °C for 8 h. The mixture was cooled to room temp. and diluted with water (75 mL).
 The organic layer was extracted with EtOAc (5 x 100 mL). The combined organic
 layers were washed with a saturated NaCl solution (200 mL), dried (MgSO₄) and

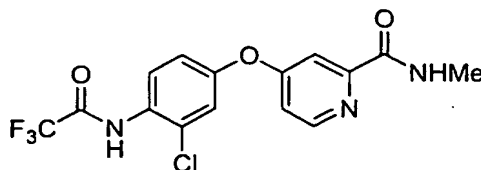
concentrated under reduced pressure. The residual black oil was treated with Et₂O (50 mL) and sonicated. The solution was then treated with HCl (1 M in Et₂O; 100 mL) and stirred at room temp. for 5 min. The resulting dark pink solid (7.04 g, 24.1 mmol) was removed by filtration from solution and stored under anaerobic conditions at 0 °C prior to use: ¹H NMR (DMSO-d₆) δ 2.41 (s, 3H), 2.78 (d, *J*=4.4 Hz, 3H), 4.93 (br s, 2H), 7.19 (dd, *J*=8.5, 2.6 Hz, 1H), 7.23 (dd, *J*=5.5, 2.6 Hz, 1H), 7.26 (d, *J*=2.6 Hz, 1H), 7.55 (d, *J*=2.6 Hz, 1H), 7.64 (d, *J*=8.8 Hz, 1H), 8.55 (d, *J*=5.9 Hz, 1H), 8.99 (q, *J*=4.8 Hz, 1H).

- 10 **A6. General Method for the Synthesis of Anilines from Hydroxyanilines by *N*-Protection, Nucleophilic Aromatic Substitution and Deprotection. Synthesis of 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline**



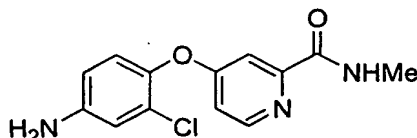
- 15 **Step 1: Synthesis of 3-Chloro-4-(2,2,2-trifluoroacetylaminophenyl)phenol**
Iron (3.24 g, 58.00 mmol) was added to stirring TFA (200 mL). To this slurry was added 2-chloro-4-nitrophenol (10.0 g, 58.0 mmol) and trifluoroacetic anhydride (20 mL). This gray slurry was stirred at room temp. for 6 d. The iron was filtered from solution and the remaining material was concentrated under reduced pressure. The resulting gray solid was dissolved in water (20 mL). To the resulting yellow solution was added a saturated NaHCO₃ solution (50 mL). The solid which precipitated from solution was removed. The filtrate was slowly quenched with the sodium bicarbonate solution until the product visibly separated from solution (determined was using a mini work-up vial). The slightly cloudy yellow solution was extracted with EtOAc (3 x 125 mL). The combined organic layers were washed with a saturated NaCl solution (125 mL), dried (MgSO₄) and concentrated under reduced pressure. The ¹H NMR (DMSO-d₆) indicated a 1:1 ratio of the nitrophenol starting material and the intended product 3-chloro-4-(2,2,2-
- 25

trifluoroacetylamino)phenol. The crude material was taken on to the next step without further purification.



5 **Step 2: Synthesis of 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chlorophenyl (222-trifluoro)acetamide**

A solution of crude 3-chloro-4-(2,2,2-trifluoroacetylamino)phenol (5.62 g, 23.46 mmol) in dry dimethylacetamide (50 mL) was treated with potassium *tert*-butoxide (5.16 g, 45.98 mmol) and the brownish black mixture was stirred at room temp.
10 until the flask had cooled to room temp. The resulting mixture was treated with 4-chloro-*N*-methyl-2-pyridinecarboxamide (Method A2, Step 3b; 1.99 g, 11.7 mmol) and heated at 100 °C under argon for 4 d. The black reaction mixture was cooled to room temp. and then poured into cold water (100 mL). The mixture was extracted with EtOAc (3 x 75 mL) and the combined organic layers were concentrated under
15 reduced pressure. The residual brown oil was purified by column chromatography (gradient from 20% EtOAc/pet. ether to 40% EtOAc/pet. ether) to yield 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chlorophenyl (222-trifluoro)acetamide as a yellow solid (8.59 g, 23.0 mmol).



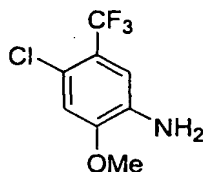
20 **Step 3. Synthesis of 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline**

A solution of crude 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chlorophenyl (222-trifluoro)acetamide (8.59 g, 23.0 mmol) in dry 4-dioxane (20 mL) was treated with a 1N NaOH solution (20 mL). This brown solution was allowed to stir for 8 h. To
25 this solution was added EtOAc (40 mL). The green organic layer was extracted with EtOAc (3 x 40 mL) and the solvent was concentrated to yield 4-(2-(*N*-

Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline as a green oil that solidified upon standing (2.86 g, 10.30 mmol): ^1H NMR (DMSO- d_6) δ 2.77 (d, $J=4.8$ Hz, 3H), 5.51 (s, 2H), 6.60 (dd, $J=8.5$, 2.6 Hz, 1H), 6.76 (d, $J=2.6$ Hz, 1H), 7.03 (d, $J=8.5$ Hz, 1H), 7.07 (dd, $J=5.5$, 2.6 Hz, 1H), 7.27 (d, $J=2.6$ Hz, 1H), 8.46 (d, $J=5.5$ Hz, 1H), 8.75 (q, $J=4.8$, 1H).

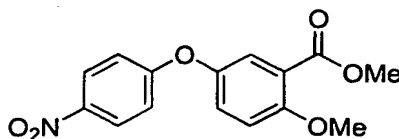
A7. General Method for the Deprotection of an Acylated Aniline.

Synthesis of 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline



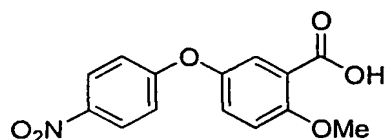
A suspension of 3-chloro-6-(N-acetyl)-4-(trifluoromethyl)anisole (4.00 g, 14.95 mmol) in a 6M HCl solution (24 mL) was heated at the reflux temp. for 1 h. The resulting solution was allowed to cool to room temp. during which time it solidified slightly. The resulting mixture was diluted with water (20 mL) then treated with a combination of solid NaOH and a saturated NaHCO_3 solution until the solution was basic. The organic layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were dried (MgSO_4) and concentrated under reduced pressure to yield 4-chloro-2-methoxy-5-(trifluoromethyl)aniline as a brown oil (3.20 g, 14.2 mmol): ^1H NMR (DMSO- d_6) δ 3.84 (s, 3H), 5.30 (s, 2H), 7.01 (s, 2H).

A8. General Method for Synthesis of ω -Alkoxy- ω -carboxyphenyl Anilines. Synthesis of 4-(3-(N-Methylcarbamoyl)-4-methoxyphenoxy)aniline.



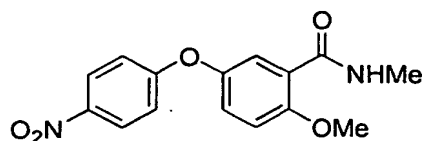
Step 1. 4-(3-Methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene:

To a solution of 4-(3-carboxy-4-hydroxyphenoxy)-1-nitrobenzene (prepared from 2,5-dihydroxybenzoic acid in a manner analogous to that described in Method A13, Step 1, 12 mmol) in acetone (50 mL) was added K_2CO_3 (5 g) and dimethyl sulfate (3.5 mL). The resulting mixture was heated at the reflux temp. overnight, then cooled to room temp. and filtered through a pad of Celite[®]. The resulting solution was concentrated under reduced pressure, absorbed onto SiO_2 , and purified by column chromatography (50% EtOAc / 50% hexane) to give 4-(3-methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene as a yellow powder (3 g): mp 115-118 °C.



10 **Step 2. 4-(3-Carboxy-4-methoxyphenoxy)-1-nitrobenzene:**

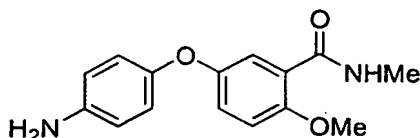
A mixture of 4-(3-methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene (1.2 g), KOH (0.33 g) and water (5 mL) in MeOH (45 mL) was stirred at room temp. overnight and then heated at the reflux temp. for 4 h. The resulting mixture was cooled to room temp. and concentrated under reduced pressure. The residue was dissolved in water (50 mL), and the aqueous mixture was made acidic with a 1N HCl solution. The resulting mixture was extracted with EtOAc (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 4-(3-carboxy-4-methoxyphenoxy)-1-nitrobenzene (1.04 g).



20 **Step 3. 4-(3-(N-Methylcarbamoyl)-4-methoxyphenoxy)-1-nitrobenzene:**

To a solution of 4-(3-carboxy-4-methoxyphenoxy)-1-nitrobenzene (0.50 g, 1.75 mmol) in CH_2Cl_2 (12 mL) was added $SOCl_2$ (0.64 mL, 8.77 mmol) in portions. The resulting solution was heated at the reflux temp. for 18 h, cooled to room temp., and concentrated under reduced pressure. The resulting yellow solids were dissolved in CH_2Cl_2 (3 mL) then the resulting solution was treated with a methylamine solution (2.0 M in THF, 3.5 mL, 7.02 mmol) in portions (CAUTION: gas evolution), and

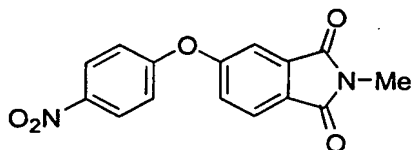
stirred at room temp. for 4 h. The resulting mixture was treated with a 1N NaOH solution, then extracted with CH₂Cl₂ (25 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to give 4-(3-(*N*-methylcarbamoyl)-4-methoxyphenoxy)-1-nitrobenzene as a yellow solid (0.50 g, 95%).



Step 4. 4-(3-(*N*-Methylcarbamoyl)-4-methoxyphenoxy)aniline:

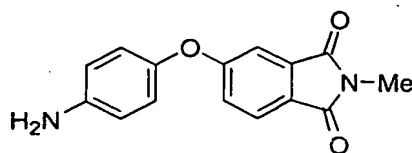
A slurry of 4-(3-(*N*-methylcarbamoyl)-4-methoxyphenoxy)-1-nitrobenzene (0.78 g, 2.60 mmol) and 10% Pd/C (0.20 g) in EtOH (55 mL) was stirred under 1 atm of H₂ (balloon) for 2.5 d, then was filtered through a pad of Celite[®]. The resulting solution was concentrated under reduced pressure to afford 4-(3-(*N*-methylcarbamoyl)-4-methoxyphenoxy)aniline as an off-white solid (0.68 g, 96%); TLC (0.1% Et₃N/99.9% EtOAc) R_f 0.36.

A9. General Method for Preparation of ω -Alkylphthalimide-containing Anilines. Synthesis of 5-(4-Aminophenoxy)-2-methylisoindoline-1,3-dione



Step 1. Synthesis of 5-(4-Nitrophenoxy)-2-methylisoindoline-1,3-dione:

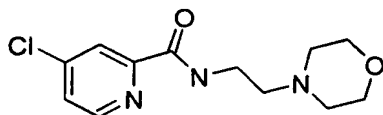
A slurry of 5-(4-nitrophenoxy)isoindoline-1,3-dione (A3 Step 2; 1.0 g, 3.52 mmol) and NaH (0.13 g, 5.27 mmol) in DMF (15 mL) was stirred at room temp. for 1 h, then treated with methyl iodide (0.3 mL, 4.57 mmol). The resulting mixture was stirred at room temp. overnight, then was cooled to °C and treated with water (10 mL). The resulting solids were collected and dried under reduced pressure to give 5-(4-nitrophenoxy)-2-methylisoindoline-1,3-dione as a bright yellow solid (0.87 g, 83%); TLC (35% EtOAc/65% hexane) R_f 0.61.



Step 2. Synthesis of 5-(4-Aminophenoxy)-2-methylisoindoline-1,3-dione:

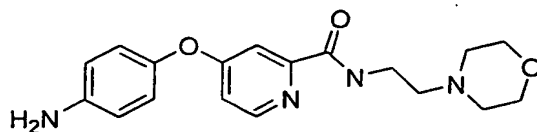
A slurry of nitrophenoxy)-2-methylisoindoline-1,3-dione (0.87 g, 2.78 mmol) and 10% Pd/C (0.10 g) in MeOH was stirred under 1 atm of H₂ (balloon) overnight. The resulting mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The resulting yellow solids were dissolved in EtOAc (3 mL) and filtered through a plug of SiO₂ (60% EtOAc/40% hexane) to afford 5-(4-aminophenoxy)-2-methylisoindoline-1,3-dione as a yellow solid (0.67 g, 86%): TLC (40% EtOAc/60% hexane) R_f 0.27.

A10. General Method for Synthesis of ω-Carbamoylaryl Anilines Through Reaction of ω-Alkoxycarbonylaryl Precursors with Amines. Synthesis of 4-(2-(N-(2-morpholin-4-ylethyl)carbamoyl)pyridyloxy)aniline



Step 1. Synthesis of 4-Chloro-2-(N-(2-morpholin-4-ylethyl)carbamoyl)pyridine

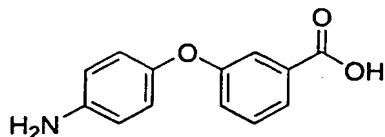
To a solution of methyl 4-chloropyridine-2-carboxylate HCl salt (Method A2, Step 2; 1.01 g, 4.86 mmol) in THF (20 mL) was added 4-(2-aminoethyl)morpholine (2.55 mL, 19.4 mmol) dropwise and the resulting solution was heated at the reflux temp. for 20 h, cooled to room temp., and treated with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to afford 4-chloro-2-(N-(2-morpholin-4-ylethyl) carbamoyl)pyridine as a yellow oil (1.25 g, 95%): TLC (10% MeOH/90% EtOAc) R_f 0.50.



Step 2. Synthesis of 4-(2-(N-(2-Morpholin-4-ylethyl)carbamoyl)pyridyloxy)aniline.

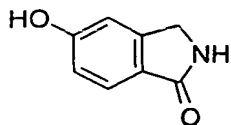
A solution of 4-aminophenol (0.49 g, 4.52 mmol) and potassium *tert*-butoxide (0.53 g, 4.75 mol) in DMF (8 mL) was stirred at room temp. for 2 h, then was sequentially treated with 4-chloro-2-(N-(2-morpholin-4-ylethyl)carbamoyl)pyridine (1.22 g, 4.52 mmol) and K₂CO₃ (0.31 g, 2.26 mmol). The resulting mixture was heated at 75 °C overnight, cooled to room temp., and separated between EtOAc (25 mL) and a saturated NaCl solution (25 mL). The aqueous layer was back extracted with EtOAc (25 mL). The combined organic layers were washed with a saturated NaCl solution (3 x 25 mL) and concentrated under reduced pressure. The resulting brown solids were purified by column chromatography (58 g; gradient from 100% EtOAc to 25% MeOH/75% EtOAc) to afford 4-(2-(N-(2-morpholin-4-ylethyl)carbamoyl)pyridyloxy)aniline (1.0 g, 65%): TLC (10% MeOH/90% EtOAc) R_f 0.32.

A11. General Method for the Reduction of Nitroarenes to Arylamines. Synthesis of 4-(3-Carboxyphenoxy)aniline.



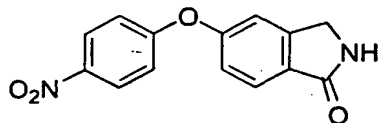
A slurry of 4-(3-carboxyphenoxy)-1-nitrobenzene (5.38 g, 20.7 mmol) and 10% Pd/C (0.50 g) in MeOH (120 mL) was stirred under an H₂ atmosphere (balloon) for 2 d. The resulting mixture was filtered through a pad of Celite®, then concentrated under reduced pressure to afford 4-(3-carboxyphenoxy)aniline as a brown solid (2.26 g, 48%): TLC (10% MeOH/90% CH₂Cl₂) R_f 0.44 (streaking).

A12. General Method for the Synthesis of Isoindolinone-Containing Anilines. Synthesis of 4-(1-Oxoisoindolin-5-yloxy)aniline.



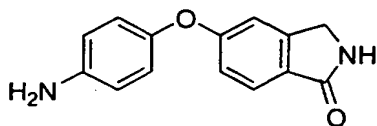
Step 1. Synthesis of 5-hydroxyisoindolin-1-one

- 5 To a solution of 5-hydroxyphthalimide (19.8 g, 121 mmol) in AcOH (500 mL) was slowly added zinc dust (47.6 g, 729 mmol) in portions, then the mixture was heated at the reflux temp. for 40 min., filtered hot, and concentrated under reduced pressure. The reaction was repeated on the same scale and the combined oily residue was purified by column chromatography (1.1 Kg SiO₂; gradient from 60% EtOAc/40% hexane to 25% MeOH/75% EtOAc) to give 5-hydroxyisoindolin-1-one (3.77 g): TLC (100% EtOAc) R_f 0.17; HPLC ES-MS *m/z* 150 ((M+H)⁺).



Step 2. Synthesis of 4-(1-isoindolinon-5-yloxy)-1-nitrobenzene

- 15 To a slurry of NaH (0.39 g, 16.1 mmol) in DMF at 0 °C was added 5-hydroxyisoindolin-1-one (2.0 g, 13.4 mmol) in portions. The resulting slurry was allowed to warm to room temp. and was stirred for 45 min., then 4-fluoro-1-nitrobenzene was added and then mixture was heated at 70 °C for 3 h. The mixture was cooled to 0 °C and treated with water dropwise until a precipitate formed. The resulting solids were collected to give 4-(1-isoindolinon-5-yloxy)-1-nitrobenzene as a dark yellow solid (3.23 g, 89%): TLC (100% EtOAc) R_f 0.35.

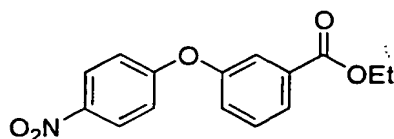


Step 3. Synthesis of 4-(1-oxoisoindolin-5-yloxy)aniline

- A slurry of 4-(1-isoindolinon-5-yloxy)-1-nitrobenzene (2.12 g, 7.8 mmol) and 10% Pd/C (0.20 g) in EtOH (50 mL) was stirred under an H₂ atmosphere (balloon) for 4 h, then filtered through a pad of Celite®. The filtrate was concentrated under
- 25

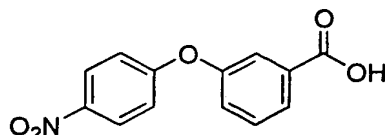
reduced pressure to afford 4-(1-oxoisindolin-5-yloxy)aniline as a dark yellow solid: TLC (100% EtOAc) R_f 0.15.

A13. General Method for the Synthesis of ω -Carbamoyl Anilines via EDCI-Mediated Amide Formation Followed by Nitroarene Reduction. Synthesis of 4-(3-*N*-Methylcarbamoylphenoxy)aniline.



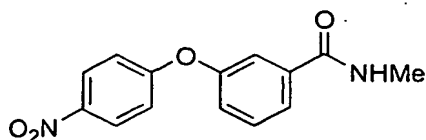
Step 1. Synthesis of 4-(3-ethoxycarbonylphenoxy)-1-nitrobenzene

10 A mixture of 4-fluoro-1-nitrobenzene (16 mL, 150 mmol), ethyl 3-hydroxybenzoate 25 g, 150 mmol) and K_2CO_3 (41 g, 300 mmol) in DMF (125 mL) was heated at the reflux temp. overnight, cooled to room temp. and treated with water (250 mL). The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic phases were sequentially washed with water (3 x 100 mL) and a saturated NaCl
15 solution (2 x 100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/90% hexane) to afford 4-(3-ethoxycarbonylphenoxy)-1-nitrobenzene as an oil (38 g).



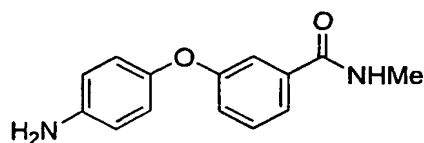
Step 2. Synthesis of 4-(3-carboxyphenoxy)-1-nitrobenzene

20 To a vigorously stirred mixture of 4-(3-ethoxycarbonylphenoxy)-1-nitrobenzene (5.14 g, 17.9 mmol) in a 3:1 THF/water solution (75 mL) was added a solution $LiOH \cdot H_2O$ (1.50 g, 35.8 mmol) in water (36 mL). The resulting mixture was heated at 50 °C overnight, then cooled to room temp., concentrated under reduced pressure, and adjusted to pH 2 with a 1M HCl solution. The resulting bright yellow solids
25 were removed by filtration and washed with hexane to give 4-(3-carboxyphenoxy)-1-nitrobenzene (4.40 g, 95%).



Step 3. Synthesis of 4-(3-(*N*-methylcarbamoyl)phenoxy)-1-nitrobenzene

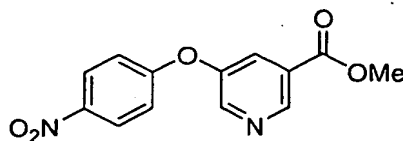
A mixture of 4-(3-carboxyphenoxy)-1-nitrobenzene (3.72 g, 14.4 mmol), EDCI·HCl (3.63 g, 18.6 mmol), *N*-methylmorpholine (1.6 mL, 14.5 mmol) and methylamine (2.0 M in THF; 8 mL, 16 mmol) in CH₂Cl₂ (45 mL) was stirred at room temp. for 3 d, then concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL) and the resulting mixture was extracted with a 1M HCl solution (50 mL). The aqueous layer was back-extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with a saturated NaCl solution (50 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give 4-(3-(*N*-methylcarbamoyl)phenoxy)-1-nitrobenzene as an oil (1.89 g).



Step 4. Synthesis of 4-(3-(*N*-methylcarbamoyl)phenoxy)aniline

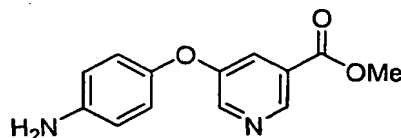
A slurry of 4-(3-(*N*-methylcarbamoyl)phenoxy)-1-nitrobenzene (1.89 g, 6.95 mmol) and 5% Pd/C (0.24 g) in EtOAc (20 mL) was stirred under an H₂ atm (balloon) overnight. The resulting mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The residue was purified by column chromatography (5% MeOH/95% CH₂Cl₂). The resulting oil solidified under vacuum overnight to give 4-(3-(*N*-methylcarbamoyl)phenoxy)aniline as a yellow solid (0.95 g, 56%).

A14. General Method for the Synthesis of ω-Carbamoyl Anilines via EDCI-Mediated Amide Formation Followed by Nitroarene Reduction.
Synthesis of 4-3-(5-Methylcarbamoyl)pyridyloxy)aniline



Step 1. Synthesis of 4-(3-(5-methoxycarbonyl)pyridyloxy)-1-nitrobenzene

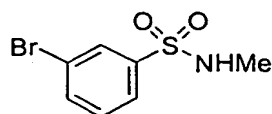
To a slurry of NaH (0.63 g, 26.1 mmol) in DMF (20 mL) was added a solution of methyl 5-hydroxynicotinate (2.0 g, 13.1 mmol) in DMF (10 mL). The resulting mixture was added to a solution of 4-fluoronitrobenzene (1.4 mL, 13.1 mmol) in DMF (10 mL) and the resulting mixture was heated at 70 °C overnight, cooled to room temp., and treated with MeOH (5 mL) followed by water (50 mL). The resulting mixture was extracted with EtOAc (100 mL). The organic phase was concentrated under reduced pressure. The residue was purified by column chromatography (30% EtOAc/70% hexane) to afford 4-(3-(5-methoxycarbonyl)pyridyloxy)-1-nitrobenzene (0.60 g).



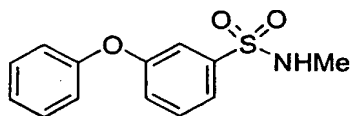
Step 2. Synthesis of 4-(3-(5-methoxycarbonyl)pyridyloxy)aniline

A slurry of 4-(3-(5-methoxycarbonyl)pyridyloxy)-1-nitrobenzene (0.60 g, 2.20 mmol) and 10% Pd/C in MeOH/EtOAc was stirred under an H₂ atmosphere (balloon) for 72 h. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 10% EtOAc/90% hexane to 30% EtOAc/70% hexane to 50% EtOAc/50% hexane) to afford 4-(3-(5-methoxycarbonyl)pyridyloxy)aniline (0.28 g, 60%): ¹H NMR (CDCl₃) δ 3.92 (s, 3H), 6.71 (d, 2H), 6.89 (d, 2H), 7.73 (, 1H), 8.51 (d, 1H), 8.87 (d, 1H).

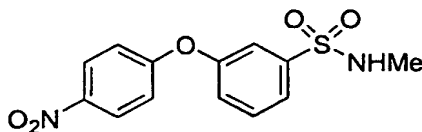
A15. Synthesis of an Aniline via Electrophilic Nitration Followed by Reduction. Synthesis of 4-(3-Methylsulfamoylphenoxy)aniline.

**Step 1. Synthesis of *N*-methyl-3-bromobenzenesulfonamide**

To a solution of 3-bromobenzenesulfonyl chloride (2.5 g, 11.2 mmol) in THF (15 mL) at 0 °C was added methylamine (2.0 M in THF; 28 mL, 56 mmol). The resulting solution was allowed to warm to room temp. and was stirred at room temp. overnight. The resulting mixture was separated between EtOAc (25 mL) and a 1 M HCl solution (25 mL). The aqueous phase was back-extracted with EtOAc (2 x 25 mL). The combined organic phases were sequentially washed with water (2 x 25 mL) and a saturated NaCl solution (25 mL), dried (MgSO₄) and concentrated under reduced pressure to give *N*-methyl-3-bromobenzenesulfonamide as a white solid (2.8 g, 99%).

**Step 2. Synthesis of 4-(3-(*N*-methylsulfamoyl)phenoxy)benzene**

To a slurry of phenol (1.9 g, 20 mmol), K₂CO₃ (6.0 g, 40 mmol), and CuI (4 g, 20 mmol) in DMF (25 mL) was added *N*-methyl-3-bromobenzenesulfonamide (2.5 g, 10 mmol), and the resulting mixture was stirred at the reflux temp. overnight, cooled to room temp., and separated between EtOAc (50 mL) and a 1 N HCl solution (50 mL). The aqueous layer was back-extracted with EtOAc (2 x 50 mL). The combined organic phases were sequentially washed with water (2 x 50 mL) and a saturated NaCl solution (50 mL), dried (MgSO₄), and concentrated under reduced pressure. The residual oil was purified by column chromatography (30% EtOAc/70% hexane) to give 4-(3-(*N*-methylsulfamoyl)phenoxy)benzene (0.30 g).

**Step 3. Synthesis of 4-(3-(*N*-methylsulfamoyl)phenoxy)-1-nitrobenzene**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: LANGE=5

In re Application of:)	Confirmation No.: 3991
)	
Robert LANGE)	Art Unit: 1774
)	
I.A. Filing Date: 02/26/2002)	Examiner: Merrick L. Dixon
371(c) Date: March 23, 2004)	
)	August 18, 2006
U.S. Appln. No.: 10/469,118)	
)	
For: MEDICAL IMPLANT)	
)	

SECOND REPLY TO FINAL ACTION: SUBMISSION OF POWER OF ATTORNEY, SECOND TERMINAL DISCLAIMER AND REMARKS

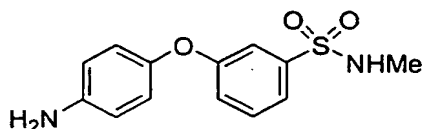
Customer Service Window, Mail Stop Amendment
Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building
401 Dulany Street
Alexandria, Virginia 22314

Sir:

This is Reply to the Final Action of April 5, 2006, and the Advisory Action of August 4, 2006. Attached is a petition for two months' extension of time and payment of the two months' late fee. No amendments are proposed.

Applicant has previously requested acknowledgement by the PTO of the receipt of applicant's papers filed under Section 11, but so far the PTO has not responded. Applicant again respectfully requests the PTO to acknowledge receipt of applicant's papers filed under §119.

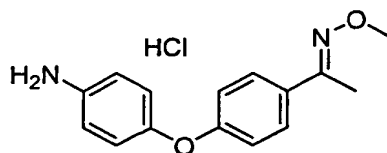
To a solution of 4-(3-(*N*-methylsulfamoyl)phenoxy)benzene (0.30 g, 1.14 mmol) in TFA (6 mL) at -10°C was added NaNO₂ (0.097 g, 1.14 mmol) in portions over 5 min. The resulting solution was stirred at -10 °C for 1 h, then was allowed to warm to room temp., and was concentrated under reduced pressure. The residue was separated between EtOAc (10 mL) and water (10 mL). The organic phase was sequentially washed with water (10 mL) and a saturated NaCl solution (10 mL), dried (MgSO₄) and concentrated under reduced pressure to give 4-(3-(*N*-methylsulfamoyl)phenoxy)-1-nitrobenzene (0.20 g). This material carried on to the next step without further purification.



Step 4. Synthesis of 4-(3-(*N*-methylsulfamoyl)phenoxy)aniline

A slurry of 4-(3-(*N*-methylsulfamoyl)phenoxy)-1-nitrobenzene (0.30 g) and 10% Pd/C (0.030 g) in EtOAc (20 mL) was stirred under an H₂ atmosphere (balloon) overnight. The resulting mixture was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (30% EtOAc/70% hexane) to give 4-(3-(*N*-methylsulfamoyl)phenoxy)aniline (0.070 g).

A16. Modification of ω-ketones. Synthesis of 4-(4-(1-(*N*-methoxy)iminoethyl)phenoxy)aniline HCl salt.

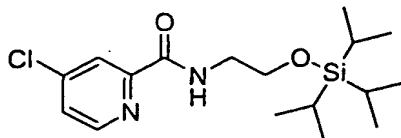


To a slurry of 4-(4-acetylphenoxy)aniline HCl salt (prepared in a manner analogous to Method A13, step 4; 1.0 g, 3.89 mmol) in a mixture of EtOH (10 mL) and pyridine (1.0 mL) was added *O*-methylhydroxylamine HCl salt (0.65 g, 7.78 mmol, 2.0 equiv.). The resulting solution was heated at the reflux temperature for 30 min, cooled to room temperature and concentrated under reduced pressure. The resulting

solids were triturated with water (10 mL) and washed with water to give 4-(4-(1-(*N*-methoxyiminoethyl) phenoxy)aniline HCl salt as a yellow solid (0.85 g): TLC (50% EtOAc/50% pet. ether) R_f 0.78; ^1H NMR (DMSO- d_6) δ 3.90 (s, 3H), 5.70 (s, 3H); HPLC-MS m/z 257 ($(\text{M}+\text{H})^+$).

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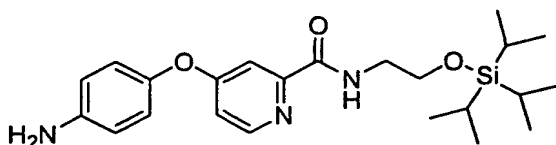
A17. Synthesis of *N*-(ω -Silyloxyalkyl)amides. Synthesis of 4-(4-(2-(*N*-(2-Triisopropylsilyloxy)ethylcarbamoyl)pyridyloxy)aniline.



Step 1. 4-Chloro-*N*-(2-triisopropylsilyloxy)ethylpyridine-2-carboxamide

To a solution of 4-chloro-*N*-(2-hydroxyethyl)pyridine-2-carboxamide (prepared in a manner analogous to Method A2, Step 3b; 1.5 g, 7.4 mmol) in anhyd DMF (7 mL) was added triisopropylsilyl chloride (1.59 g, 8.2 mmol, 1.1 equiv.) and imidazole (1.12 g, 16.4 mmol, 2.2 equiv.). The resulting yellow solution was stirred for 3 h at room temp, then was concentrated under reduced pressure. The residue was separated between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (MgSO_4), and concentrated under reduced pressure to afford 4-chloro-2-(*N*-(2-triisopropylsilyloxy)ethyl)pyridinecarboxamide as an orange oil (2.32 g, 88%). This material was used in the next step without further purification.

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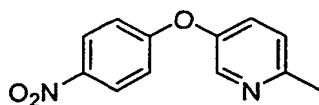
Step 2. 4-(4-(2-(*N*-(2-Triisopropylsilyloxy)ethylcarbamoyl)pyridyloxy)aniline

To a solution of 4-hydroxyaniline (0.70 g, 6.0 mmol) in anhyd DMF (8 mL) was added potassium *tert*-butoxide (0.67 g, 6.0 mmol, 1.0 equiv.) in one portion causing an exotherm. When this mixture had cooled to room temperature, a solution of 4-chloro-2-(*N*-(2-triisopropylsilyloxy)ethyl)pyridinecarboxamide (2.32 g, 6 mmol, 1

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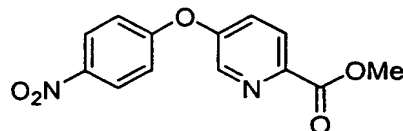
equiv.) in DMF (4 mL) was added followed by K_2CO_3 (0.42 g, 3.0 mmol, 0.50 equiv.). The resulting mixture was heated at 80 °C overnight. An additional portion of potassium *tert*-butoxide (0.34 g, 3 mmol, 0.5 equiv.) was then added and the mixture was stirred at 80 °C an additional 4 h. The mixture was cooled to 0 °C with an ice/water bath, then water (approx. 1 mL) was slowly added dropwise. The organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The brown oily residue was purified by column chromatography (SiO_2 ; 30% EtOAc/ 70% pet ether) to afford 4-(4-(2-(*N*-(2-triisopropylsilyloxy)ethylcarbamoyl)pyridyloxy)aniline as a clear light brown oil (0.99 g, 38%).

A18. Synthesis of 2-Pyridinecarboxylate Esters via Oxidation of 2-Methylpyridines. Synthesis of 4-(5-(2-methoxycarbonyl)pyridyloxy)aniline.



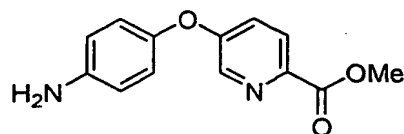
Step 1. 4-(5-(2-Methyl)pyridyloxy)-1-nitrobenzene.

A mixture of 5-hydroxy-2-methylpyridine (10.0 g, 91.6 mmol), 1-fluoro-4-nitrobenzene (9.8 mL, 91.6 mmol, 1.0 equiv.), K_2CO_3 (25 g, 183 mmol, 2.0 equiv.) in DMF (100 mL) was heated at the reflux temperature overnight. The resulting mixture was cooled to room temperature, treated with water (200 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layers were sequentially washed with water (2 x 100 mL) and a saturated NaCl solution ((100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give 4-(5-(2-methyl)pyridyloxy)-1-nitrobenzene as a brown solid (12.3 g).



Step 2. Synthesis of 4-(5-(2-Methoxycarbonyl)pyridyloxy)-1-nitrobenzene.

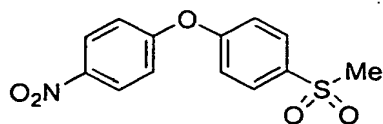
A mixture of 4-(5-(2-methyl)pyridyloxy)-1-nitrobenzene (1.70 g, 7.39 mmol) and selenium dioxide (2.50 g, 22.2 mmol, 3.0 equiv.) in pyridine (20 mL) was heated at the reflux temperature for 5 h, then cooled to room temperature. The resulting slurry was filtered, then concentrated under reduced pressure. The residue was dissolved in MeOH (100 mL). The solution was treated with a conc HCl solution (7 mL), then heated at the reflux temperature for 3 h, cooled to room temperature and concentrated under reduced pressure. The residue was separated between EtOAc (50 mL) and a 1N NaOH solution (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were sequentially washed with water (2 x 50 mL) and a saturated NaCl solution (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂; 50% EtOAc/50% hexane) to afford 4-(5-(2-methoxycarbonyl)pyridyloxy)-1-nitrobenzene (0.70 g).



Step 3. Synthesis of 4-(5-(2-Methoxycarbonyl)pyridyloxy)aniline.

A slurry of 4-(5-(2-methoxycarbonyl)pyridyloxy)-1-nitrobenzene (0.50 g) and 10% Pd/C (0.050 g) in a mixture of EtOAc (20 mL) and MeOH (5 mL) was placed under a H₂ atmosphere (balloon) overnight. The resulting mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂; 70% EtOAc/30% hexane) to give 4-(5-(2-methoxycarbonyl)pyridyloxy)aniline (0.40 g).

A19. Synthesis of ω -Sulfonylphenyl Anilines. Synthesis of 4-(4-Methylsulfonylphenoxy)aniline.

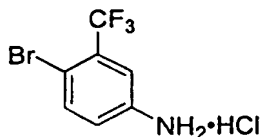


Step 1. 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene: To a solution of 4-(4-methylthiophenoxy)-1-nitrobenzene (2.0 g, 7.7 mmol) in CH_2Cl_2 (75 mL) at 0 °C was slowly added *m*-CPBA (57-86%, 4.0 g), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was treated with a 1N NaOH solution (25 mL). The organic layer was sequentially washed with a 1N NaOH solution (25 mL), water (25 mL) and a saturated NaCl solution (25 mL), dried (MgSO_4), and concentrated under reduced pressure to give 4-(4-methylsulfonylphenoxy)-1-nitrobenzene as a solid (2.1 g).

Step 2. 4-(4-Methylsulfonylphenoxy)-1-aniline: 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene was reduced to the aniline in a manner analogous to that described in Method A18, step 3.

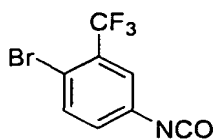
B. Synthesis of Urea Precursors

B1. General Method for the Synthesis of Isocyanates from Anilines Using CDI. Synthesis of 4-Bromo-3-(trifluoromethyl)phenyl Isocyanate.



Step 1. Synthesis of 4-bromo-3-(trifluoromethyl)aniline HCl salt

To a solution of 4-bromo-3-(trifluoromethyl)aniline (64 g, 267 mmol) in Et_2O (500 mL) was added an HCl solution (1 M in Et_2O ; 300 mL) dropwise and the resulting mixture was stirred at room temp. for 16 h. The resulting pink-white precipitate was removed by filtration and washed with Et_2O (50 mL) and to afford 4-bromo-3-(trifluoromethyl)aniline HCl salt (73 g, 98%).

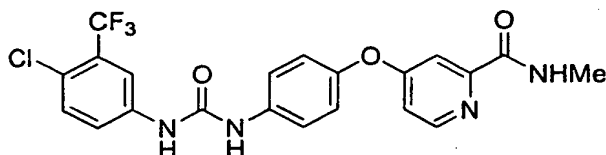


Step 2. Synthesis of 4-bromo-3-(trifluoromethyl)phenyl isocyanate

A suspension of 4-bromo-3-(trifluoromethyl)aniline HCl salt (36.8 g, 133 mmol) in toluene (278 mL) was treated with trichloromethyl chloroformate dropwise and the resulting mixture was heated at the reflux temp. for 18 h. The resulting mixture was concentrated under reduced pressure. The residue was treated with toluene (500 mL), then concentrated under reduced pressure. The residue was treated with CH₂Cl₂ (500 mL), then concentrated under reduced pressure. The CH₂Cl₂ treatment/concentration protocol was repeated and resulting amber oil was stored at -20 °C for 16 h, to afford 4-bromo-3-(trifluoromethyl)phenyl isocyanate as a tan solid (35.1 g, 86%): GC-MS *m/z* 265 (M⁺).

C. Methods of Urea Formation

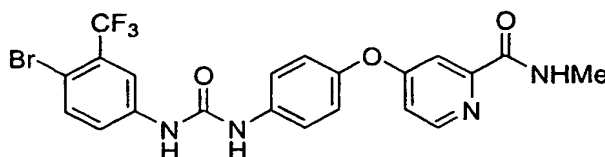
C1a. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea



A solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (14.60 g, 65.90 mmol) in CH₂Cl₂ (35 mL) was added dropwise to a suspension of 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (Method A2, Step 4; 16.0 g, 65.77 mmol) in CH₂Cl₂ (35 mL) at 0 °C. The resulting mixture was stirred at room temp. for 22 h. The resulting yellow solids were removed by filtration, then washed with CH₂Cl₂ (2 x 30 mL) and dried under reduced pressure (approximately 1 mmHg) to afford *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as an off-white solid (28.5 g, 93%): mp 207-209 °C; ¹H-

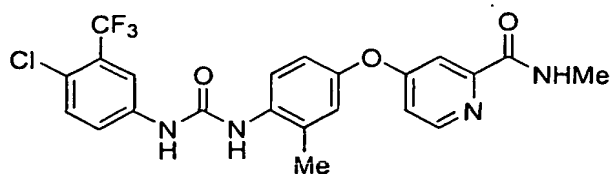
NMR (DMSO- d_6) δ 2.77 (d, $J=4.8$ Hz, 3H), 7.16 (m, 3H), 7.37 (d, $J=2.5$ Hz, 1H), 7.62 (m, 4H), 8.11 (d, $J=2.5$ Hz, 1H), 8.49 (d, $J=5.5$ Hz, 1H), 8.77 (br d, 1H), 8.99 (s, 1H), 9.21 (s, 1H); HPLC ES-MS m/z 465 ((M+H) $^+$).

- 5 **C1b.** **General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of *N*-(4-Bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea**



- 10 A solution of 4-bromo-3-(trifluoromethyl)phenyl isocyanate (Method B1, Step 2; 8.0 g, 30.1 mmol) in CH_2Cl_2 (80 mL) was added dropwise to a solution of 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (Method A2, Step 4; 7.0 g, 28.8 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The resulting mixture was stirred at room temp. for 16 h. The resulting yellow solids were removed by filtration, then washed with CH_2Cl_2 (2
15 x 50 mL) and dried under reduced pressure (approximately 1 mmHg) at 40 °C to afford *N*-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as a pale-yellow solid (13.2 g, 90%): mp 203-205 °C; 1H -NMR (DMSO- d_6) δ 2.77 (d, $J=4.8$ Hz, 3H), 7.16 (m, 3H), 7.37 (d, $J=2.5$ Hz, 1H), 7.58 (m, 3H), 7.77 (d, $J=8.8$ Hz, 1H), 8.11 (d, $J=2.5$ Hz, 1H), 8.49 (d, $J=5.5$ Hz,
20 1H), 8.77 (br d, 1H), 8.99 (s, 1H), 9.21 (s, 1H); HPLC ES-MS m/z 509 ((M+H) $^+$).

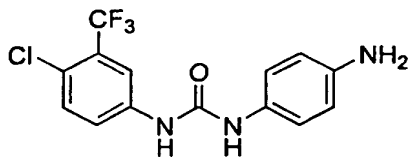
- 25 **C1c.** **General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(2-methyl-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) Urea**



A solution of 2-methyl-4-(2-(N-methylcarbamoyl)(4-pyridyloxy))aniline (Method A5; 0.11 g, 0.45 mmol) in CH_2Cl_2 (1 mL) was treated with Et_3N (0.16 mL) and 4-chloro-3-(trifluoromethyl)phenyl isocyanate (0.10 g, 0.45 mmol). The resulting brown solution was stirred at room temp. for 6 d, then was treated with water (5 mL). The aqueous layer was back-extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (MgSO_4) and concentrated under reduced pressure to yield

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(2-methyl-4-(2-(N-methylcarbamoyl)(4-pyridyloxy))phenyl) urea as a brown oil (0.11 g, 0.22 mmol): ^1H NMR ($\text{DMSO}-d_6$) δ 2.27 (s, 3H), 2.77 (d, $J=4.8$ Hz, 3H), 7.03 (dd, $J=8.5, 2.6$ Hz, 1H), 7.11 (d, $J=2.9$ Hz, 1H), 7.15 (dd, $J=5.5, 2.6$ Hz, 1H), 7.38 (d, $J=2.6$ Hz, 1H), 7.62 (app d, $J=2.6$ Hz, 2H), 7.84 (d, $J=8.8$ Hz, 1H), 8.12 (s, 1H), 8.17 (s, 1H); 8.50 (d, $J=5.5$ Hz, 1H), 8.78 (q, $J=5.2$, 1H), 9.52 (s, 1H); HPLC ES-MS m/z 479 ($(\text{M}+\text{H})^+$).

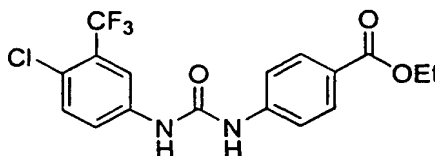
C1d. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-aminophenyl) Urea



To a solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (2.27 g, 10.3 mmol) in CH_2Cl_2 (308 mL) was added *p*-phenylenediamine (3.32 g, 30.7 mmol) in one part. The resulting mixture was stirred at room temp. for 1 h, treated with CH_2Cl_2 (100 mL), and concentrated under reduced pressure. The resulting pink solids were dissolved in a mixture of EtOAc (110 mL) and MeOH (15mL), and the clear solution was washed with a 0.05 N HCl solution. The organic layer was

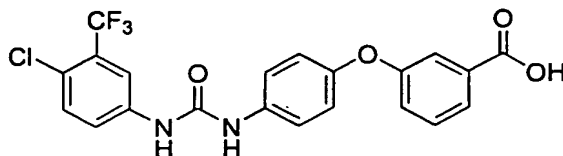
concentrated under reduced pressure to afford impure *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-aminophenyl) urea (3.3 g): TLC (100% EtOAc) R_f 0.72.

5 **C1e. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-ethoxycarbonylphenyl) Urea**



10 To a solution of ethyl 4-isocyanatobenzoate (3.14 g, 16.4 mmol) in CH_2Cl_2 (30 mL) was added 4-chloro-3-(trifluoromethyl)aniline (3.21 g, 16.4 mmol), and the solution was stirred at room temp. overnight. The resulting slurry was diluted with CH_2Cl_2 (50 mL) and filtered to afford *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-ethoxycarbonylphenyl) urea as a white solid (5.93 g, 97%): TLC (40% EtOAc/60% hexane) R_f 0.44.

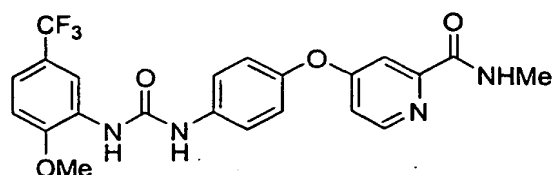
15 **C1f. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-carboxyphenyl) Urea**



20 To a solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (1.21g, 5.46 mmol) in CH_2Cl_2 (8 mL) was added 4-(3-carboxyphenoxy)aniline (Method A11; 0.81 g, 5.76 mmol) and the resulting mixture was stirred at room temp. overnight, then treated with MeOH (8 mL), and stirred an additional 2 h. The resulting mixture was concentrated under reduced pressure. The resulting brown solids were triturated with a 1:1 EtOAc/hexane solution to give *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-carboxyphenyl) urea as an off-white solid (1.21 g, 76%).

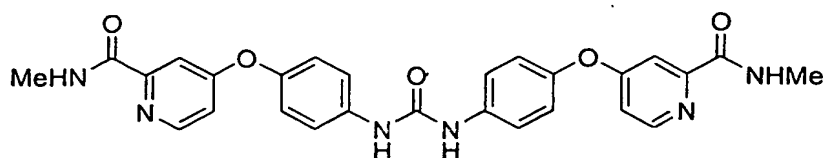
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C2a. General Method for Urea Synthesis by Reaction of an Aniline with *N,N'*-Carbonyl Diimidazole Followed by Addition of a Second Aniline. Synthesis of *N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea



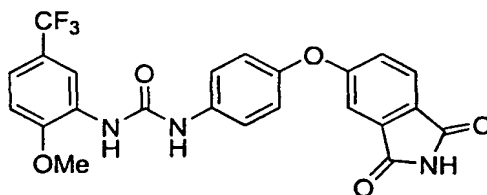
To a solution of 2-methoxy-5-(trifluoromethyl)aniline (0.15 g) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added CDI (0.13 g). The resulting solution was allowed to warm to room temp. over 1 h, was stirred at room temp. for 16 h, then was treated with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (0.18 g). The resulting yellow solution was stirred at room temp. for 72 h, then was treated with H_2O (125 mL). The resulting aqueous mixture was extracted with EtOAc (2 x 150 mL). The combined organics were washed with a saturated NaCl solution (100 mL), dried (MgSO_4) and concentrated under reduced pressure. The residue was triturated (90% EtOAc/10% hexane). The resulting white solids were collected by filtration and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residual oil purified by column chromatography (gradient from 33% EtOAc/67% hexane to 50% EtOAc/50% hexane to 100% EtOAc) to give *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as a light tan solid (0.098 g, 30%): TLC (100% EtOAc) R_f 0.62; ^1H NMR ($\text{DMSO}-d_6$) δ 2.76 (d, $J=4.8$ Hz, 3H), 3.96 (s, 3H), 7.1-7.6 and 8.4-8.6 (m, 11H), 8.75 (d, $J=4.8$ Hz, 1H), 9.55 (s, 1 H); FAB-MS m/z 461 ($(\text{M}+\text{H})^+$).

C2b. General Method for Urea Synthesis by Reaction of an Aniline with *N,N'*-Carbonyl Diimidazole Followed by Addition of a Second Aniline. Symmetrical Urea's as Side Products of a *N,N'*-Carbonyl Diimidazole Reaction Procedure. Synthesis of Bis(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea



To a stirring solution of 3-amino-2-methoxyquinoline (0.14 g) in anhydrous CH_2Cl_2 (15 mL) at 0 C was added CDI (0.13 g). The resulting solution was allowed to warm to room temp. over 1 h then was stirred at room temp. for 16 h. The resulting mixture was treated with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (0.18 g). The resulting yellow solution stirred at room temp. for 72 h, then was treated with water (125 mL). The resulting aqueous mixture was extracted with EtOAc (2 x 150 mL). The combined organic phases were washed with a saturated NaCl solution (100 ml), dried (MgSO_4) and concentrated under reduced pressure. The residue was triturated (90% EtOAc/10% hexane). The resulting white solids were collected by filtration and washed with EtOAc to give bis(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea (0.081 g, 44%): TLC (100% EtOAc) R_f 0.50; ^1H NMR ($\text{DMSO}-d_6$) δ 2.76 (d, $J=5.1$ Hz, 6H), 7.1-7.6 (m, 12H), 8.48 (d, $J=5.4$ Hz, 1H), 8.75 (d, $J=4.8$ Hz, 2H), 8.86 (s, 2H); HPLC ES-MS m/z 513 ($(\text{M}+\text{H})^+$).

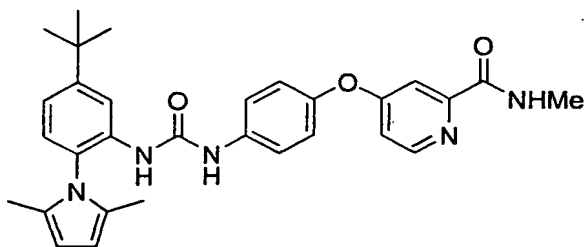
C2c. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of *N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(1,3-dioxoisindolin-5-yloxy)phenyl) Urea



To a stirring solution of 2-methoxy-5-(trifluoromethyl)phenyl isocyanate (0.10 g, 0.47 mmol) in CH_2Cl_2 (1.5 mL) was added 5-(4-aminophenoxy)isindoline-1,3-dione (Method A3, Step 3; 0.12 g, 0.47 mmol) in one portion. The resulting mixture was stirred for 12 h, then was treated with CH_2Cl_2 (10 mL) and MeOH (5 mL). The resulting mixture was sequentially washed with a 1N HCl solution (15 mL) and a

saturated NaCl solution (15 mL), dried (MgSO₄) and concentrated under reduced pressure to afford *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(1,3-dioxoisindolin-5-yloxy)phenyl) urea as a white solid (0.2 g, 96%): TLC (70% EtOAc/30% hexane) *R_f* 0.50; ¹H NMR (DMSO-*d*₆) δ 3.95 (s, 3H), 7.31-7.10 (m, 6H), 7.57 (d, *J*=9.3Hz, 2H), 7.80 (d, *J*=8.7 Hz, 1H), 8.53 (br s, 2H), 9.57 (s, 1H), 11.27 (br s, 1H); HPLC ES-MS 472.0 ((*M*+*H*)⁺, 100%).

C2d. General Method for Urea Synthesis by Reaction of an Aniline with *N,N'*-Carbonyl Diimidazole Followed by Addition of a Second Aniline. Synthesis of *N*-(5-(*tert*-Butyl)-2-(2,5-dimethylpyrrolyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea



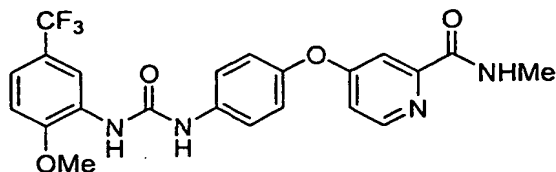
To a stirring solution of CDI (0.21g, 1.30 mmol) in CH₂Cl₂ (2 mL) was added 5-(*tert*-butyl)-2-(2,5-dimethylpyrrolyl)aniline (Method A4, Step 2; 0.30 g, 1.24 mmol) in one portion. The resulting mixture was stirred at room temp. for 4 h, then 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (0.065 g, 0.267mmol) was then added in one portion. The resulting mixture was heated at 36 °C overnight, then cooled to room temp. and diluted with EtOAc (5 mL). The resulting mixture was sequentially washed with water (15 mL) and a 1N HCl solution (15mL), dried (MgSO₄), and filtered through a pad of silica gel (50 g) to afford *N*-(5-(*tert*-butyl)-2-(2,5-dimethylpyrrolyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as a yellowish solid (0.033 g, 24%): TLC (40% EtOAc/60% hexane) *R_f* 0.24; ¹H NMR (acetone-*d*₆) δ 1.37 (s, 9H), 1.89 (s, 6H), 2.89 (d, *J*=4.8Hz, 3H), 5.83 (s, 2H), 6.87-7.20 (m, 6H), 7.17 (dd, 1H), 7.51-7.58 (m, 3H), 8.43 (d, *J*=5.4Hz, 1H), 8.57 (d, *J*=2.1Hz, 1H), 8.80 (br s, 1H); HPLC ES-MS 512 ((*M*+*H*)⁺, 100%).

C3. Combinatorial Method for the Synthesis of Diphenyl Ureas Using Triphosgene

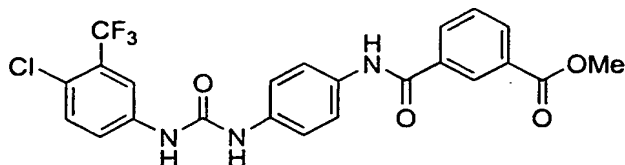
One of the anilines to be coupled was dissolved in dichloroethane (0.10 M). This solution was added to a 8 mL vial (0.5 mL) containing dichloroethane (1 mL). To this was added a bis(trichloromethyl) carbonate solution (0.12 M in dichloroethane, 0.2 mL, 0.4 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.). The vial was capped and heat at 80 °C for 5 h, then allowed to cool to room temp for approximately 10 h. The second aniline was added (0.10 M in dichloroethane, 0.5 mL, 1.0 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.). The resulting mixture was heated at 80 °C for 4 h, cooled to room temperature and treated with MeOH (0.5 mL). The resulting mixture was concentrated under reduced pressure and the products were purified by reverse phase HPLC.

C4. General Method for Urea Synthesis by Reaction of an Aniline with Phosgene Followed by Addition of a Second Aniline.

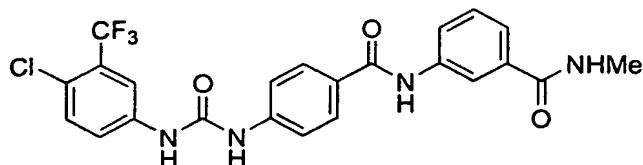
Synthesis of *N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea



To a stirring solution of phosgene (1.9 M in toluene; 2.07 mL 0.21 g, 1.30 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added anhydrous pyridine (0.32 mL) followed by 2-methoxy-5-(trifluoromethyl)aniline (0.75 g). The yellow solution was allowed to warm to room temp during which a precipitate formed. The yellow mixture was stirred for 1 h, then concentrated under reduced pressure. The resulting solids were treated with anhydrous toluene (20 mL) followed by 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (prepared as described in Method A2; 0.30 g) and the resulting suspension was heated at 80 °C for 20 h, then allowed to cool to room temp. The resulting mixture was diluted with water (100 mL), then was made basic with a saturated NaHCO_3 solution (2-3 mL). The basic solution was extracted with EtOAc (2 x 250 mL). The organic layers were separately washed with a saturated NaCl solution, combined, dried (MgSO_4), and concentrated under reduced pressure. The resulting pink-brown residue was dissolved in MeOH and absorbed onto SiO_2 (100 g). Column chromatography (300 g SiO_2 ; gradient from 1% Et_3N /33% EtOAc/66% hexane to 1% Et_3N /99% EtOAc to 1% Et_3N /20% MeOH/79% EtOAc) followed by concentration under reduced pressure at 45 °C gave a warm concentrated EtOAc solution, which was treated with hexane (10 mL) to slowly form crystals of *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea (0.44 g): TLC (1% Et_3N /99% EtOAc) R_f 0.40.

D. Interconversion of Ureas**D1a. Conversion of ω -Aminophenyl Ureas into ω -(Aroylamino)phenyl Ureas. Synthesis of *N*-(4-Chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-methoxycarbonylphenyl)carboxyaminophenyl) Urea**

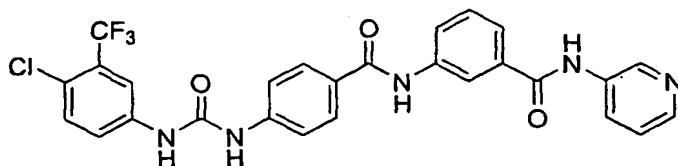
To a solution of *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-aminophenyl) urea (Method C1d; 0.050 g, 1.52 mmol), *mono*-methyl isophthalate (0.25 g, 1.38 mmol), HOBT·H₂O (0.41 g, 3.03 mmol) and *N*-methylmorpholine (0.33 mL, 3.03 mmol) in DMF (8 mL) was added EDCI ·HCl (0.29 g, 1.52 mmol). The resulting mixture was stirred at room temp. overnight, diluted with EtOAc (25 mL) and sequentially washed with water (25 mL) and a saturated NaHCO₃ solution (25 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The resulting solids were triturated with an EtOAc solution (80% EtOAc/20% hexane) to give *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-methoxycarbonylphenyl)carboxyaminophenyl) urea (0.27 g, 43%); mp 121-122; TLC (80% EtOAc/20% hexane) R_f 0.75.

D1b. Conversion of ω -Carboxyphenyl Ureas into ω -(Arylcarbamoyl)phenyl Ureas. Synthesis of *N*-(4-Chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-methylcarbamoylphenyl)carbamoylphenyl) Urea

To a solution of *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-methylcarbamoylphenyl) carboxyaminophenyl) urea (0.14 g, 0.48 mmol), 3-methylcarbamoylaniline (0.080 g, 0.53 mmol), HOBT·H₂O (0.14 g, 1.07 mmol),

and *N*-methylmorpholine (0.5 mL, 1.07 mmol) in DMF (3 mL) at 0 °C was added EDCI•HCl (0.10 g, 0.53 mmol). The resulting mixture was allowed to warm to room temp. and was stirred overnight. The resulting mixture was treated with water (10 mL), and extracted with EtOAc (25 mL). The organic phase was concentrated under reduced pressure. The resulting yellow solids were dissolved in EtOAc (3 mL) then filtered through a pad of silica gel (17 g, gradient from 70% EtOAc/30% hexane to 10% MeOH/90% EtOAc) to give *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-methylcarbamoylphenyl) carbamoylphenyl) urea as a white solid (0.097 g, 41%): mp 225-229; TLC (100% EtOAc) R_f 0.23.

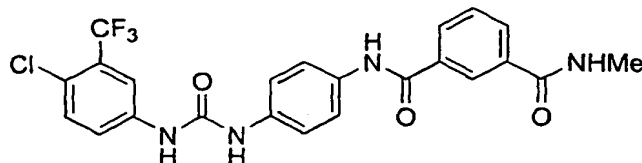
D1c. Combinatorial Approach to the Conversion of ω -Carboxyphenyl Ureas into ω -(Arylcarbamoyl)phenyl Ureas. Synthesis of *N*-(4-Chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(*N*-(3-(*N*-(3-pyridyl)carbamoyl)phenyl)carbamoyl)phenyl) Urea



A mixture of *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(3-carboxyphenyl) urea (Method C1f; 0.030 g, 0.067 mmol) and *N*-cyclohexyl-*N'*-(methylpolystyrene)carbodiimide (55 mg) in 1,2-dichloroethane (1 mL) was treated with a solution of 3-aminopyridine in CH₂Cl₂ (1 M; 0.074 mL, 0.074 mmol). (In cases of insolubility or turbidity, a small amount of DMSO was also added.) The resulting mixture was heated at 36 °C overnight. Turbid reactions were then treated with THF (1 mL) and heating was continued for 18 h. The resulting mixtures were treated with poly(4-(isocyanatomethyl)styrene) (0.040 g) and the resulting mixture was stirred at 36 °C for 72 h, then cooled to room temp. and filtered. The resulting solution was filtered through a plug of silica gel (1 g). Concentration under reduced pressure afforded *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(*N*-(3-(*N*-(3-

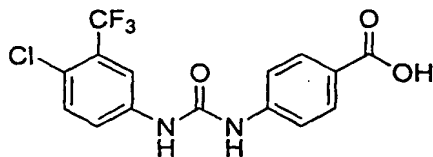
pyridyl)carbamoyl)phenyl)carbamoyl)phenyl) urea (0.024 g, 59%): TLC (70% EtOAc/30% hexane) R_f 0.12.

D2. Conversion of ω -Carboalkoxyaryl Ureas into ω -Carbamoylaryl Ureas. Synthesis of *N*-(4-Chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-methylcarbamoylphenyl)carboxyaminophenyl) Urea



To a sample of *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-carbomethoxyphenyl) carboxyaminophenyl) urea (0.17 g, 0.34 mmol) was added methylamine (2 M in THF; 1 mL, 1.7 mmol) and the resulting mixture was stirred at room temp. overnight, then concentrated under reduced pressure to give *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-methylcarbamoylphenyl)carboxyaminophenyl) urea as a white solid: mp 247; TLC (100% EtOAc) R_f 0.35.

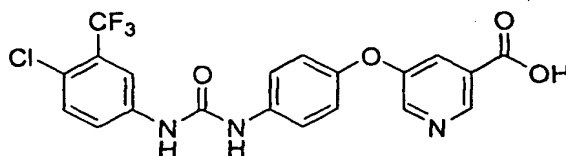
D3. Conversion of ω -Carboalkoxyaryl Ureas into ω -Carboxyaryl Ureas. Synthesis of *N*-(4-Chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-carboxyphenyl) Urea



To a slurry of *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-ethoxycarbonylphenyl) urea (Method C1e; 5.93 g, 15.3 mmol) in MeOH (75 mL) was added an aqueous KOH solution (2.5 N, 10 mL, 23 mmol). The resulting mixture was heated at the reflux temp. for 12 h, cooled to room temp., and concentrated under reduced pressure. The residue was diluted with water (50 mL), then treated with a 1 N HCl solution to adjust the pH to 2 to 3. The resulting solids were collected and dried

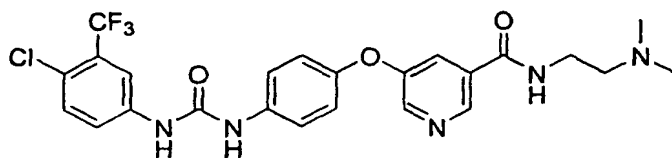
under reduced pressure to give *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-carboxyphenyl) urea as a white solid (5.05 g, 92%).

D4. General Method for the Conversion of ω -Alkoxy Esters into ω -Alkyl Amides. Synthesis of *N*-(4-Chloro-3-((trifluoromethyl)phenyl)-*N'*-((4-(3-(5-(2-dimethylaminoethyl)carbamoyl)pyridyl)oxyphenyl) Urea



Step 1. Synthesis of *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-carboxypyridyl) oxyphenyl) Urea

N-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-methoxycarbonylpyridyl) oxyphenyl) urea was synthesized from 4-chloro-3-(trifluoromethyl)phenyl isocyanate and 4-(3-(5-methoxycarbonylpyridyl) oxyaniline (Method A14, Step 2) in a manner analogous to Method C1a. A suspension of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-methoxycarbonylpyridyl)oxyphenyl) urea (0.26 g, 0.56 mmol) in MeOH (10 mL) was treated with a solution of KOH (0.14 g, 2.5 mmol) in water (1 mL) and was stirred at room temp. for 1 h. The resulting mixture was adjusted to pH 5 with a 1 N HCl solution. The resulting precipitate was removed by filtration and washed with water. The resulting solids were dissolved in EtOH (10 mL) and the resulting solution was concentrated under reduced pressure. The EtOH/concentration procedure was repeated twice to give *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-carboxypyridyl) oxyphenyl) urea (0.18 g, 71%).

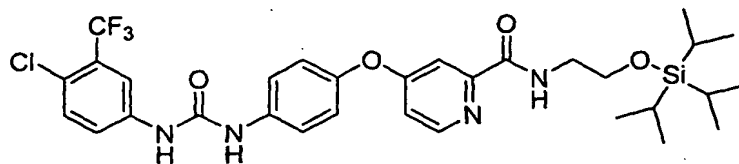


Step 2. Synthesis of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-(2-dimethylaminoethyl)carbamoyl)pyridyl)oxyphenyl) urea

A mixture of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-carboxypyridyl) oxyphenyl) urea (0.050 g, 0.011 mmol), *N,N*-dimethylethylenediamine (0.22 mg,

0.17 mmol), HOBT (0.028 g, 0.17 mmol), *N*-methylmorpholine (0.035 g, 0.28 mmol), and EDCI·HCl (0.032 g, 0.17 mmol) in DMF (2.5 mL) was stirred at room temp. overnight. The resulting solution was separated between EtOAc (50 mL) and water (50 mL). The organic phase was washed with water (35 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was dissolved in a minimal amount of CH₂Cl₂ (approximately 2 mL). The resulting solution was treated with Et₂O dropwise to give *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-(2-dimethylaminoethyl)carbamoyl) pyridyl)oxyphenyl) urea as a white precipitate (0.48 g, 84%: ¹H NMR (DMSO-*d*₆) δ 2.10 (s, 6H), 3.26 (s, H), 7.03 (d, 2H), 7.52 (d, 2H), 7.60 (m, 3H), 8.05 (s, 1H), 8.43 (s, 1H), 8.58 (t, 1H), 8.69 (s, 1H), 8.90 (s, 1H), 9.14 (s, 1H); HPLC ES-MS *m/z* 522 ((M+H)⁺).

D5. General Method for the Deprotection of *N*-(ω-Silyloxyalkyl)amides. Synthesis of *N*-(4-Chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(4-(2-(*N*-(2-hydroxy)ethylcarbamoyl)pyridyloxyphenyl) Urea.



To a solution of *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(4-(2-(*N*-(2-triisopropylsilyloxy) ethylcarbamoyl)pyridyloxyphenyl) urea (prepared in a manner analogous to Method C1a; 0.25 g, 0.37 mmol) in anhyd THF (2 mL) was tetrabutylammonium fluoride (1.0 M in THF; 2 mL). The mixture was stirred at room temperature for 5 min, then was treated with water (10 mL). The aqueous mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂; gradient from 100% hexane to 40% EtOAc/60% hexane) to give *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(4-(2-(*N*-(2-hydroxy)ethylcarbamoyl) pyridyloxyphenyl) urea as a white solid (0.019 g, 10%).

Listed below are compounds listed in the Tables below which have been synthesized according to the Detailed Experimental Procedures given above:

Syntheses of Exemplified Compounds

(see Tables for compound characterization)

5 Entry 1: 4-(3-*N*-Methylcarbamoylphenoxy)aniline was prepared according to Method A13. According to Method C3, 3-*tert*-butylaniline was reacted with bis(trichloromethyl)carbonate followed by 4-(3-*N*-Methylcarbamoylphenoxy)aniline
10 to afford the urea.

Entry 2: 4-Fluoro-1-nitrobenzene and *p*-hydroxyacetophenone were reacted according to Method A13, Step 1 to afford the 4-(4-acetylphenoxy)-1-nitrobenzene. 4-(4-Acetylphenoxy)-1-nitrobenzene was reduced according to Method A13, Step 4
15 to afford 4-(4-acetylphenoxy)aniline. According to Method C3, 3-*tert*-butylaniline was reacted with bis(trichloromethyl) carbonate followed by 4-(4-acetylphenoxy)aniline to afford the urea.

Entry 3: According to Method C2d, 3-*tert*-butylaniline was treated with CDI,
20 followed by 4-(3-*N*-methylcarbamoyl)-4-methoxyphenoxy)aniline, which had been prepared according to Method A8, to afford the urea.

Entry 4: 5-*tert*-Butyl-2-methoxyaniline was converted to 5-*tert*-butyl-2-methoxyphenyl isocyanate according to Method B1. 4-(3-*N*-
25 Methylcarbamoylphenoxy)aniline, prepared according to Method A13, was reacted with the isocyanate according to Method C1a to afford the urea.

Entry 5: According to Method C2d, 5-*tert*-butyl-2-methoxyaniline was reacted with CDI followed by 4-(3-*N*-methylcarbamoyl)-4-methoxyphenoxy)aniline, which had
30 been prepared according to Method A8, to afford the urea.

Entry 6: 5-(4-Aminophenoxy)isoindoline-1,3-dione was prepared according to Method A3. According to Method 2d, 5-*tert*-butyl-2-methoxyaniline was reacted with CDI followed by 5-(4-aminophenoxy)isoindoline-1,3-dione to afford the urea.

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Entry 7: 4-(1-Oxoisindolin-5-yloxy)aniline was synthesized according to Method A12. According to Method 2d, 5-*tert*-butyl-2-methoxyaniline was reacted with CDI followed by 4-(1-oxoisindolin-5-yloxy)aniline to afford the urea.

10 Entry 8: 4-(3-*N*-Methylcarbamoylphenoxy)aniline was synthesized according to Method A13. According to Method C2a, 2-methoxy-5-(trifluoromethyl)aniline was reacted with CDI followed by 4-(3-*N*-methylcarbamoylphenoxy)aniline to afford the urea.

15 Entry 9: 4-Hydroxyacetophenone was reacted with 2-chloro-5-nitropyridine to give 4-(4-acetylphenoxy)-5-nitropyridine according to Method A3, Step 2. According to Method A8, Step 4, 4-(4-acetylphenoxy)-5-nitropyridine was reduced to 4-(4-acetylphenoxy)-5-aminopyridine. 2-Methoxy-5-(trifluoromethyl)aniline was converted to 2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method

20 B1. The isocyanate was reacted with 4-(4-acetylphenoxy)-5-aminopyridine according to Method C1a to afford the urea.

Entry 10: 4-Fluoro-1-nitrobenzene and *p*-hydroxyacetophenone were reacted according to Method A13, Step 1 to afford the 4-(4-acetylphenoxy)-1-nitrobenzene.

25 4-(4-Acetylphenoxy)-1-nitrobenzene was reduced according to Method A13, Step 4 to afford 4-(4-acetylphenoxy)aniline. According to Method C3, 5-(trifluoromethyl)-2-methoxybutylaniline was reacted with bis(trichloromethyl) carbonate followed by 4-(4-acetylphenoxy)aniline to afford the urea.

Entry 11: 4-Chloro-*N*-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline. According to Method C4, 2-methoxy-5-(trifluoromethyl)aniline was reacted with phosgene followed by 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 12: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with ammonia according to Method A2, Step 3b to form 4-chloro-2-pyridinecarboxamide. 4-Chloro-2-pyridinecarboxamide was reacted with 3-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 3-(2-carbamoyl-4-pyridyloxy)aniline. According to Method C2a, 2-methoxy-5-(trifluoromethyl)aniline was reacted with phosgene followed by 3-(2-carbamoyl-4-pyridyloxy)aniline to afford the urea.

Entry 13: 4-Chloro-*N*-methyl-2-pyridinecarboxamide was synthesized according to Method A2, Step 3b. 4-Chloro-*N*-methyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline. According to Method C2a, 2-methoxy-5-(trifluoromethyl)aniline was reacted with CDI followed by 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 14: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with ammonia according to Method A2, Step 3b to form 4-chloro-2-pyridinecarboxamide. 4-Chloro-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 4-(2-carbamoyl-4-pyridyloxy)aniline. According to Method C4, 2-methoxy-5-(trifluoromethyl)aniline was reacted with phosgene followed by 4-(2-carbamoyl-4-pyridyloxy)aniline to afford the urea.

Entry 15: According to Method C2d, 5-(trifluoromethyl)-2-methoxyaniline was reacted with CDI followed by 4-(3-*N*-methylcarbamoyl)-4-methoxyphenoxy)aniline, which had been prepared according to Method A8, to afford the urea.

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Entry 16: 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-methylaniline was synthesized according to Method A5. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. The isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-2-methylaniline according to Method C1c to afford the urea.

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Entry 17: 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline was synthesized according to Method A6. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline according to Method C1a to afford the urea.

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Entry 18: According to Method A2, Step 4, 5-amino-2-methylphenol was reacted with 4-chloro-*N*-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-4-methylaniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-4-methylaniline according to Method C1a to afford the urea.

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Entry 19: 4-Chloropyridine-2-carbonyl chloride was reacted with ethylamine according to Method A2, Step 3b. The resulting 4-chloro-*N*-ethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2,

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Step 4 to give 4-(2-(*N*-ethylcarbamoyl)-4-pyridyloxy)aniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(2-(*N*-ethylcarbamoyl)-4-pyridyloxy)aniline according to Method C1a to afford the urea.

Entry 20: According to Method A2, Step 4, 4-amino-2-chlorophenol was reacted with 4-chloro-*N*-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-3-chloroaniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-3-chloroaniline according to Method C1a to afford the urea.

Entry 21: 4-(4-Methylthiophenoxy)-1-nitrobenzene was oxidized according to Method A19, Step 1 to give 4-(4-methylsulfonylphenoxy)-1-nitrobenzene. The nitrobenzene was reduced according to Method A19, Step 2 to give 4-(4-methylsulfonylphenoxy)-1-aniline. According to Method C1a, 5-(trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(4-methylsulfonylphenoxy)-1-aniline to afford the urea.

Entry 22: 4-(3-carbamoylphenoxy)-1-nitrobenzene was reduced to 4-(3-carbamoylphenoxy)aniline according to Method A15, Step 4. According to Method C1a, 5-(trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(3-carbamoylphenoxy)aniline to afford the urea.

Entry 23: 5-(4-Aminophenoxy)isoindoline-1,3-dione was synthesized according to Method A3. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-

(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 5-(4-aminophenoxy)isoindoline-1,3-dione according to Method C1a to afford the urea.

Entry 24: 4-Chloropyridine-2-carbonyl chloride was reacted with dimethylamine according to Method A2, Step 3b. The resulting 4-chloro-*N,N*-dimethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(*N,N*-dimethylcarbamoyl)-4-pyridyloxy)aniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(2-(*N,N*-dimethylcarbamoyl)-4-pyridyloxy)aniline according to Method C1a to afford the urea.

Entry 25: 4-(1-Oxoisindolin-5-yloxy)aniline was synthesized according to Method A12. 5-(Trifluoromethyl)-2-methoxyaniline was treated with CDI, followed by 4-(1-oxoisindolin-5-yloxy)aniline according to Method C2d to afford the urea.

Entry 26: 4-Hydroxyacetophenone was reacted with 4-fluoronitrobenzene according to Method A13, Step 1 to give 4-(4-acetylphenoxy)nitrobenzene. The nitrobenzene was reduced according to Method A13, Step 4 to afford 4-(4-acetylphenoxy)aniline, which was converted to the 4-(4-(1-(*N*-methoxy)iminoethyl)phenoxy)aniline HCl salt according to Method A16. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(4-(1-(*N*-methoxy)iminoethyl)phenoxy)aniline HCl salt to Method C1a to afford the urea.

Entry 27: 4-Chloro-*N*-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 4-aminothiophenol according to Method A2, Step 4 to give 4-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline. 5-(Trifluoromethyl)-2-methoxyaniline was

converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline according to Method C1a to afford the urea.

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Entry 28: 5-(4-Aminophenoxy)-2-methylisoindoline-1,3-dione was synthesized according to Method A9. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 5-(4-aminophenoxy)-2-methylisoindoline-1,3-dione according to Method C1a to afford the urea.

Entry 29: 4-Chloro-*N*-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 3-aminothiophenol according to Method A2, Step 4 to give 3-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 3-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline according to Method C1a to afford the urea.

Entry 30: 4-Chloropyridine-2-carbonyl chloride was reacted with isopropylamine according to Method A2, Step 3b. The resulting 4-chloro-*N*-isopropyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(*N*-isopropylcarbamoyl)-4-pyridyloxy)aniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(2-(*N*-isopropylcarbamoyl)-4-pyridyloxy)aniline according to Method C1a to afford the urea.

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Entry 31: 4-(3-(5-Methoxycarbonyl)pyridyloxy)aniline was synthesized according to Method A14. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyloxy)aniline according to Method C1a to afford the urea. *N*-(5-(Trifluoromethyl)-2-methoxyphenyl)-*N'*-(4-(3-(5-methoxycarbonylpyridyl)oxy)phenyl) urea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with 4-(2-aminoethyl)morpholine to afford the amide according to Method D4, Step 2.

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Entry 32: 4-(3-(5-Methoxycarbonyl)pyridyloxy)aniline was synthesized according to Method A14. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyloxy)aniline according to Method C1a to afford the urea. *N*-(5-(Trifluoromethyl)-2-methoxyphenyl)-*N'*-(4-(3-(5-methoxycarbonylpyridyl)oxy)phenyl) urea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with methylamine according to Method D4, Step 2 to afford the amide.

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Entry 33: 4-(3-(5-Methoxycarbonyl)pyridyloxy)aniline was synthesized according to Method A14. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyloxy)aniline according to Method C1a to afford the urea. *N*-(5-(Trifluoromethyl)-2-methoxyphenyl)-*N'*-(4-(3-(5-methoxycarbonylpyridyl)oxy)phenyl) urea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with *N,N*-dimethylethylenediamine according to Method D4, Step 2 to afford the amide.

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Entry 34: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxy)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford *N*-(5-(trifluoromethyl)-2-methoxyphenyl)-*N'*-(3-carboxyphenyl) urea, which was coupled with 3-aminopyridine according to Method D1c.

Entry 35: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxy)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford *N*-(5-(trifluoromethyl)-2-methoxyphenyl)-*N'*-(3-carboxyphenyl) urea, which was coupled with *N*-(4-fluorophenyl)piperazine according to Method D1c.

Entry 36: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxy)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford *N*-(5-(trifluoromethyl)-2-methoxyphenyl)-*N'*-(3-carboxyphenyl) urea, which was coupled with 4-fluoroaniline according to Method D1c.

Entry 37: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxy)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford *N*-(5-(trifluoromethyl)-2-methoxyphenyl)-*N'*-(3-

carboxyphenyl) urea, which was coupled with 4-(dimethylamino)aniline according to Method D1c.

Entry 38: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11.

5 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxy)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford *N*-(5-(trifluoromethyl)-2-methoxyphenyl)-*N'*-(3-carboxyphenyl) urea, which was coupled with 5-amino-2-methoxypyridine
10 according to Method D1c.

Entry 39: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11.

5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxy)aniline
15 was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford *N*-(5-(trifluoromethyl)-2-methoxyphenyl)-*N'*-(3-carboxyphenyl) urea, which was coupled with 4-morpholinoaniline according to Method D1c.

20 Entry 40: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11.

5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxy)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford *N*-(5-(trifluoromethyl)-2-methoxyphenyl)-*N'*-(3-
25 carboxyphenyl) urea, which was coupled with *N*-(2-pyridyl)piperazine according to Method D1c.

Entry 41: 4-(3-(*N*-Methylcarbamoylethoxy)phenoxy)aniline was synthesized according to Method A13. According to Method C3, 4-chloro-3-(trifluoromethyl)aniline was

converted to the isocyanate, then reacted with 4-(3-(*N*-Methylcarbamoyl)phenoxy)aniline to afford the urea.

5 Entry 42: 4-(2-*N*-Methylcarbamyl-4-pyridyloxy)aniline was synthesized according to Method A2. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-*N*-methylcarbamyl-4-pyridyloxy)aniline according to Method C1a to afford the urea.

10 Entry 43: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with ammonia according to Method A2, Step 3b to form 4-chloro-2-pyridinecarboxamide. 4-Chloro-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to form 4-(2-carbamoyl-4-pyridyloxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-carbamoyl-4-pyridyloxy)aniline to afford the urea.

15 Entry 44: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with ammonia according to Method A2, Step 3b to form 4-chloro-2-pyridinecarboxamide. 4-Chloro-2-pyridinecarboxamide was reacted with 3-aminophenol according to Method A2, Step 4 to form 3-(2-carbamoyl-4-pyridyloxy)aniline. According to
20 Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-carbamoyl-4-pyridyloxy)aniline to afford the urea.

Entry 45: 4-Chloro-*N*-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-aminophenol according to
25 Method A2, Step 4 to form 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 46: 5-(4-Aminophenoxy)isoindoline-1,3-dione was synthesized according to
30 Method A3. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl

isocyanate was reacted with 5-(4-aminophenoxy)isoindoline-1,3-dione to afford the urea.

Entry 47: 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-methylaniline was synthesized according to Method A5. According to Method C1c, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 5-(4-aminophenoxy)isoindoline-1,3-dione to afford the urea.

Entry 48: 4-(3-*N*-Methylsulfamoyl)phenoxy)aniline was synthesized according to Method A15. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-*N*-methylsulfamoyl)phenoxy)aniline to afford the urea.

Entry 49: 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline was synthesized according to Method A6. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline to afford the urea.

Entry 50: According to Method A2, Step 4, 5-amino-2-methylphenol was reacted with 4-chloro-*N*-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-4-methylaniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-4-methylaniline to afford the urea.

Entry 51: 4-Chloropyridine-2-carbonyl chloride was reacted with ethylamine according to Method A2, Step 3b. The resulting 4-chloro-*N*-ethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(*N*-ethylcarbamoyl)-4-pyridyloxy)aniline. According to Method

C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-ethylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 52: According to Method A2, Step 4, 4-amino-2-chlorophenol was reacted with 4-chloro-*N*-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-3-chloroaniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-3-chloroaniline to afford the urea.

Entry 53: 4-(4-Methylthiophenoxy)-1-nitrobenzene was oxidized according to Method A19, Step 1 to give 4-(4-methylsulfonylphenoxy)-1-nitrobenzene. The nitrobenzene was reduced according to Method A19, Step 2 to give 4-(4-methylsulfonylphenoxy)-1-aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-methylsulfonylphenoxy)-1-aniline to afford the urea.

Entry 54: 4-Bromobenzenesulfonyl chloride was reacted with methylamine according to Method A15, Step 1 to afford *N*-methyl-4-bromobenzenesulfonamide. *N*-Methyl-4-bromobenzenesulfonamide was coupled with phenol according to Method A15, Step 2 to afford 4-(4-(*N*-methylsulfamoyl)phenoxy)benzene. 4-(4-(*N*-Methylsulfamoyl)phenoxy)benzene was converted into 4-(4-(*N*-methylsulfamoyl)phenoxy)-1-nitrobenzene according to Method A15, Step 3. 4-(4-(*N*-Methylsulfamoyl)phenoxy)-1-nitrobenzene was reduced to 4-(4-(*N*-methylsulfamoyl)phenoxy)aniline according to Method A15, Step 4. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(*N*-methylsulfamoyl)phenoxy)aniline to afford the urea.

Entry 55: 5-Hydroxy-2-methylpyridine was coupled with 1-fluoro-4-nitrobenzene according to Method A18, Step 1 to give 4-(5-(2-Methyl)pyridyloxy)-1-

nitrobenzene. The methylpyridine was oxidized according to the carboxylic acid, then esterified according to Method A18, Step 2 to give 4-(5-(2-methoxycarbonyl)pyridyloxy)-1-nitrobenzene. The nitrobenzene was reduced according the Method A18, Step 3 to give 4-(5-(2-methoxycarbonyl)pyridyloxy)aniline. The aniline was reacted with 4-chloro-3-(trifluoromethyl)phenyl isocyanate according to Method C1a to afford the urea.

Entry 56: 5-Hydroxy-2-methylpyridine was coupled with 1-fluoro-4-nitrobenzene according to Method A18, Step 1 to give 4-(5-(2-Methyl)pyridyloxy)-1-nitrobenzene. The methylpyridine was oxidized according to the carboxylic acid, then esterified according to Method A18, Step 2 to give 4-(5-(2-methoxycarbonyl)pyridyloxy)-1-nitrobenzene. The nitrobenzene was reduced according the Method A18, Step 3 to give 4-(5-(2-methoxycarbonyl)pyridyloxy)aniline. The aniline was reacted with 4-chloro-3-(trifluoromethyl)phenyl isocyanate according to Method C1a to give *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(methoxycarbonyl)-5-pyridyloxy)phenyl) urea. The methyl ester was reacted with methylamine according to Method D2 to afford *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-5-pyridyloxy)phenyl) urea.

Entry 57: *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-aminophenyl) urea was prepared according to Method C1d. *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-aminophenyl) urea was coupled with *mono*-methyl isophthalate according to Method D1a to afford the urea.

Entry 58: *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-aminophenyl) urea was prepared according to Method C1d. *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-aminophenyl) urea was coupled with *mono*-methyl isophthalate according to Method D1a to afford *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(3-methoxycarbonylphenyl)carboxyaminophenyl) urea. According to Method D2, *N*-

(4-chloro-3-(trifluoromethyl)phenyl-*N'*-(4-(3-methoxycarbonylphenyl)carboxyaminophenyl) urea was reacted with methylamine to afford the corresponding methyl amide.

5 Entry 59: 4-Chloropyridine-2-carbonyl chloride was reacted with dimethylamine according to Method A2, Step 3b. The resulting 4-chloro-*N,N*-dimethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(*N,N*-dimethylcarbamoyl)-4-pyridyloxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-
10 (*N,N*-dimethylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 60: 4-Hydroxyacetophenone was reacted with 4-fluoronitrobenzene according to Method A13, Step 1 to give 4-(4-acetylphenoxy)nitrobenzene. The nitrobenzene was reduced according to Method 13, Step 4 to afford 4-(4-acetylphenoxy)aniline,
15 which was converted to the 4-(4-(1-(*N*-methoxy)iminoethyl) phenoxy)aniline HCl salt according to Method A16. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-acetylphenoxy)aniline to afford the urea.

20 Entry 61: 4-(3-Carboxyphenoxy)-1-nitrobenzene was synthesized according to Method A13, Step 2. 4-(3-Carboxyphenoxy)-1-nitrobenzene was coupled with 4-(2-aminoethyl)morpholine according to Method A13, Step 3 to give 4-(3-(*N*-(2-morpholinylethyl)carbamoyl)phenoxy)-1-nitrobenzene. According to Method A13 Step 4, 4-(3-(*N*-(2-morpholinylethyl)carbamoyl)phenoxy)-1-nitrobenzene was
25 reduced to 4-(3-(*N*-(2-morpholinylethyl)carbamoyl)phenoxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(*N*-(2-morpholinylethyl)carbamoyl)phenoxy)aniline to afford the urea.

Entry 62: 4-(3-Carboxyphenoxy)-1-nitrobenzene was synthesized according to
30 Method A13, Step 2. 4-(3-Carboxyphenoxy)-1-nitrobenzene was coupled with 1-

(2-aminoethyl)piperidine according to Method A13, Step 3 to give 4-(3-(*N*-(2-piperidylethyl)carbamoyl)phenoxy)-1-nitrobenzene. According to Method A13 Step 4, 4-(3-(*N*-(2-piperidylethyl)carbamoyl)phenoxy)-1-nitrobenzene was reduced to 4-(3-(*N*-(2-piperidylethyl)carbamoyl)phenoxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(*N*-(2-piperidylethyl)carbamoyl)phenoxy)aniline to afford the urea.

Entry 63: 4-(3-Carboxyphenoxy)-1-nitrobenzene was synthesized according to Method A13, Step 2. 4-(3-Carboxyphenoxy)-1-nitrobenzene was coupled with tetrahydrofurfurylamine according to Method A13, Step 3 to give 4-(3-(*N*-(tetrahydrofurylmethyl)carbamoyl)phenoxy)-1-nitrobenzene. According to Method A13 Step 4, 4-(3-(*N*-(tetrahydrofurylmethyl)carbamoyl)phenoxy)-1-nitrobenzene was reduced to 4-(3-(*N*-(tetrahydrofurylmethyl)carbamoyl)phenoxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(*N*-(tetrahydrofurylmethyl)carbamoyl)phenoxy)aniline to afford the urea.

Entry 64: 4-(3-Carboxyphenoxy)-1-nitrobenzene was synthesized according to Method A13, Step 2. 4-(3-Carboxyphenoxy)-1-nitrobenzene was coupled with 2-aminomethyl-1-ethylpyrrolidine according to Method A13, Step 3 to give 4-(3-(*N*-((1-methylpyrrolidinyl)methyl)carbamoyl)phenoxy)-1-nitrobenzene. According to Method A13 Step 4, 4-(3-(*N*-((1-methylpyrrolidinyl)methyl)carbamoyl)phenoxy)-1-nitrobenzene was reduced to 4-(3-(*N*-((1-methylpyrrolidinyl)methyl)carbamoyl)phenoxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(*N*-((1-methylpyrrolidinyl)methyl)carbamoyl)phenoxy)aniline to afford the urea.

Entry 65: 4-Chloro-*N*-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 4-aminothiophenol according to Method A2, Step 4 to give 4-(4-(2-(*N*-

methylcarbamoyl)phenylthio)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline to afford the urea.

- 5 Entry 66: 4-Chloropyridine-2-carbonyl chloride was reacted with isopropylamine according to Method A2, Step 3b. The resulting 4-chloro-*N*-isopropyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(*N*-isopropylcarbamoyl)-4-pyridyloxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-
10 (*N*-isopropylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

- Entry 67: *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-ethoxycarbonylphenyl) urea was synthesized according to Method C1e. *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-ethoxycarbonylphenyl) urea was saponified
15 according to Method D3 to give *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-carboxyphenyl) urea. *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-carboxyphenyl) urea was coupled with 3-methylcarbamoylaniline according to Method D1b to give *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(3-methylcarbamoylphenyl)carbamoylphenyl) urea.

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- Entry 68: 5-(4-Aminophenoxy)-2-methylisoindoline-1,3-dione was synthesized according to Method A9. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 5-(4-aminophenoxy)-2-methylisoindoline-1,3-dione to afford the urea.

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- Entry 69: 4-Chloro-*N*-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 3-aminothiophenol according to Method A2, Step 4 to give 3-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline. According to Method C1a, 4-chloro-3-

(trifluoromethyl)phenyl isocyanate was reacted with 3-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline to afford the urea.

Entry 70: 4-(2-(*N*-(2-Morpholin-4-ylethyl)carbamoyl)pyridyloxy)aniline was synthesized according to Method A10. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-(2-morpholin-4-ylethyl)carbamoyl)pyridyloxy)aniline to afford the urea.

Entry 71: 4-(3-(5-Methoxycarbonyl)pyridyloxy)aniline was synthesized according to Method A14. 4-Chloro-3-(trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyloxy)aniline according to Method C1a to afford the urea. *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(3-(5-methoxycarbonylpyridyl)oxy)phenyl) urea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with 4-(2-aminoethyl)morpholine to afford the amide.

Entry 72: 4-(3-(5-Methoxycarbonyl)pyridyloxy)aniline was synthesized according to Method A14. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyloxy)aniline according to Method C1a to afford the urea. *N*-(5-(Trifluoromethyl)-2-methoxyphenyl)-*N'*-(4-(3-(5-methoxycarbonylpyridyl)oxy)phenyl) urea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with methylamine according to Method D4, Step 2 to afford the amide.

Entry 73: 4-(3-(5-Methoxycarbonyl)pyridyloxy)aniline was synthesized according to Method A14. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyloxy)aniline according to Method C1a to afford the urea. *N*-(5-(Trifluoromethyl)-2-methoxyphenyl)-*N'*-(4-(3-(5-methoxycarbonylpyridyl)oxy)phenyl) urea was saponified according to Method D4,

Step 1, and the corresponding acid was coupled with *N,N*-dimethylethylenediamine according to Method D4, Step 2 to afford the amide.

- Entry 74: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with 2-hydroxyethylamine according to Method A2, Step 3b to form 4-chloro-*N*-(2-triisopropylsilyloxy)ethylpyridine-2-carboxamide. 4-Chloro-*N*-(2-triisopropylsilyloxy)ethylpyridine-2-carboxamide was reacted with triisopropylsilyl chloride, followed by 4-aminophenol according to Method A17 to form 4-(4-(2-(*N*-(2-triisopropylsilyloxy)ethylcarbamoyl)pyridyloxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-(2-(*N*-(2-triisopropylsilyloxy)ethylcarbamoyl)pyridyloxy)aniline to afford *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(4-(2-(*N*-(2-triisopropylsilyloxy)ethylcarbamoyl)pyridyloxy)phenyl) urea.
- Entry 75: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(methoxycarbonyl)pyridyloxy)aniline according to Method C1f to afford the urea, which was coupled with 3-aminopyridine according to Method D1c.
- Entry 76: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with *N*-(4-acetylphenyl)piperazine according to Method D1c.
- Entry 77: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 4-fluoroaniline according to Method D1c.

Entry 78: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 4-(dimethylamino)aniline according to Method D1c.

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Entry 79: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with *N*-phenylethylenediamine according to Method D1c.

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Entry 80: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 2-methoxyethylamine according to Method D1c.

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Entry 81: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 5-amino-2-methoxypyridine according to Method D1c.

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Entry 82: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 4-morpholinoaniline according to Method D1c.

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Entry 83: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with *N*-(2-pyridyl)piperazine according to Method D1c.

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Entry 84: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with 2-hydroxyethylamine according to Method A2, Step 3b to form 4-chloro-*N*-(2-triisopropylsilyloxy)ethylpyridine-2-carboxamide.

4-Chloro-*N*-(2-triisopropylsilyloxy)ethylpyridine-2-carboxamide was reacted with triisopropylsilyl chloride, followed by 4-aminophenol according to Method A17 to form 4-(4-(2-(*N*-(2-triisopropylsilyloxy)ethylcarbamoyl)pyridyloxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-(2-(*N*-(2-triisopropylsilyloxy)ethylcarbamoyl)pyridyloxy)aniline to give *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(4-(2-(*N*-(2-triisopropylsilyloxy)ethylcarbamoyl)pyridyloxy)phenyl) urea. The urea was deprotected according to Method D5 to afford *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(4-(2-(*N*-(2-hydroxy)ethylcarbamoyl)pyridyloxy)phenyl) urea.

Entry 85: 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)aniline was synthesized according to Method A2. 4-Bromo-3-(trifluoromethyl)aniline was converted to 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 86: 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline was synthesized according to Method A6. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline to afford the urea.

Entry 87: According to Method A2, Step 4, 4-amino-2-chlorophenol was reacted with 4-chloro-*N*-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-3-chloroaniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-

(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-3-chloroaniline to afford the urea.

- 5 Entry 88: 4-Chloropyridine-2-carbonyl chloride was reacted with ethylamine according to Method A2, Step 3b. The resulting 4-chloro-*N*-ethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(*N*-ethylcarbamoyl)-4-pyridyloxy)aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-ethylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

- 15 Entry 89: 4-Chloro-*N*-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-aminophenol according to Method A2, Step 4 to form 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

- 25 Entry 90: According to Method A2, Step 4, 5-amino-2-methylphenol was reacted with 4-chloro-*N*-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-4-methylaniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-4-methylaniline to afford the urea.

Entry 91: 4-Chloropyridine-2-carbonyl chloride was reacted with dimethylamine according to Method A2, Step 3b. The resulting 4-chloro-*N,N*-dimethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(*N,N*-dimethylcarbamoyl)-4-pyridyloxy)aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N,N*-dimethylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 92: 4-Chloro-*N*-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 4-aminothiophenol according to Method A2, Step 4 to give 4-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline to afford the urea.

Entry 93: 4-Chloro-*N*-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 3-aminothiophenol according to Method A2, Step 4 to give 3-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(4-(2-(*N*-methylcarbamoyl)phenylthio)aniline to afford the urea.

Entry 94: 4-(2-(*N*-(2-Morpholin-4-ylethyl)carbamoyl)pyridyloxy)aniline was synthesized according to Method A10. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was

reacted with 4-(2-(*N*-(2-Morpholin-4-ylethyl)carbamoyl)pyridyloxy)aniline to afford the urea.

Entry 95: 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)aniline was synthesized according to Method A2. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 96: 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline was synthesized according to Method A6. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline to afford the urea.

Entry 97: According to Method A2, Step 4, 4-amino-2-chlorophenol was reacted with 4-chloro-*N*-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-3-chloroaniline. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)-3-chloroaniline to afford the urea.

Entry 98: 4-Chloro-*N*-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-aminophenol according to Method A2, Step 4 to form 3-(-2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate as was reacted with 3-(-2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 99: 4-Chloropyridine-2-carbonyl chloride was reacted with ethylamine according to Method A2, Step 3b. The resulting 4-chloro-*N*-ethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(*N*-ethylcarbamoyl)-4-pyridyloxy)aniline. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N*-ethylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 100: 4-Chloropyridine-2-carbonyl chloride was reacted with dimethylamine according to Method A2, Step 3b. The resulting 4-chloro-*N,N*-dimethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(*N,N*-dimethylcarbamoyl)-4-pyridyloxy)aniline. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(*N,N*-dimethylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

Entry 101: 4-Chloro-*N*-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-aminophenol according to Method A2, Step 4 to form 3-(-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline. 2-Amino-3-methoxynaphthalene was synthesized as described Method A1.
5 According to Method C3, 2-amino-3-methoxynaphthalene was reacted with bis(trichloromethyl) carbonate followed by 3-(-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline to form the urea.

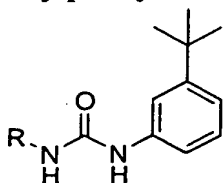
Entry 102: 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)aniline was synthesized according to Method A2. 5-*tert*-Butyl-2-(2,5-dimethylpyrrolyl)aniline was synthesized according to Method A4. 5-*tert*-Butyl-2-(2,5-dimethylpyrrolyl)aniline was reacted with CDI followed by 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline according to Method C2d to afford the urea.

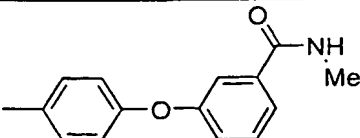
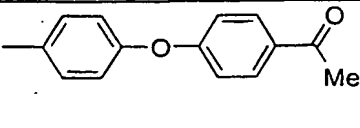
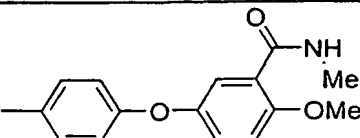
Entry 103: 4-Chloro-*N*-methyl-2-pyridinecarboxamide was synthesized according to Method A2, Step 3b. 4-Chloro-*N*-methyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline. According to Method C2b, reaction of 3-amino-2-methoxyquinoline with CDI followed by 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline afforded bis(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl)urea.

Tables

The compounds listed in Tables 1-6 below were synthesized according to the general methods shown above, and the more detailed exemplary procedures are in the entry listings above and characterizations are indicated in the tables.

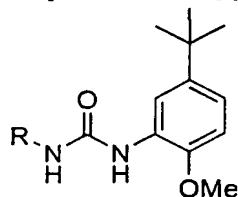
Table 1. 3-*tert*-Butylphenyl Ureas



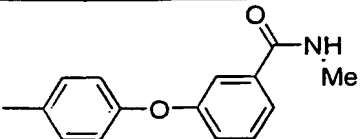
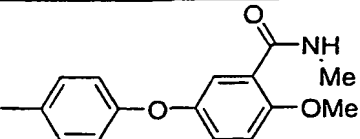
Entry	R	mp (°C)	HPLC (min.)	TLC R _f	TLC Solvent System	Mass Spec. [Source]	Synth. Method
1				0.22	50% EtOAc / 50% hexane	418 (M+H)+ (HPLC ES-MS)	A13 C3
2				0.58	50% EtOAc / 50% hexane	403 (M+H)+ (HPLC ES-MS)	A13 C3
3		133- 135		0.68	100% EtOAc	448 (M+H)+ (FAB)	A8 C2d

5

Table 2.

5-*tert*-Butyl-2-methoxyphenyl Ureas

10

Entry	R	mp (°C)	HPLC (min.)	TL C R _f	TLC Solvent System	Mass Spec. [Source]	Synth. Method
4			5.93			448 (M+H)+ (HPLC ES-MS)	A13 B1 C1a
5		120- 122		0.67	100% EtOAc	478 (M+H)+ (FAB)	A8 C2d

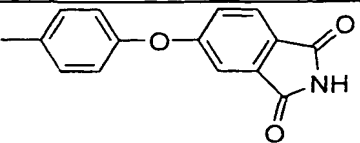
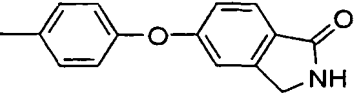
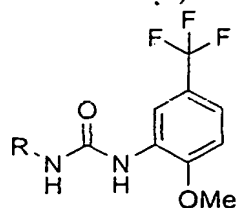
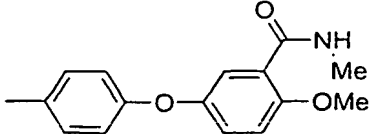
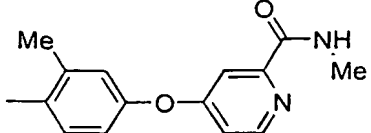
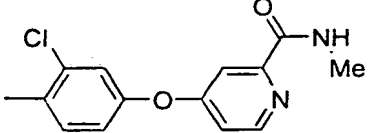
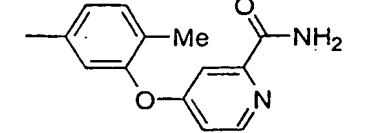
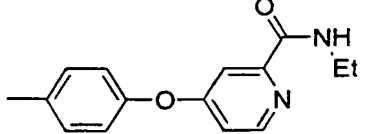
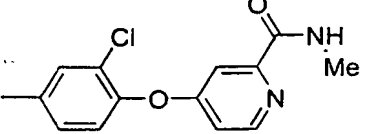
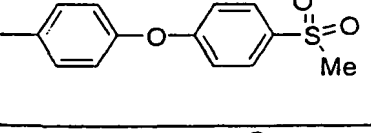
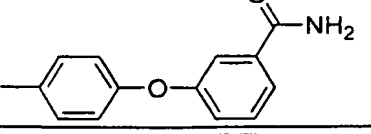
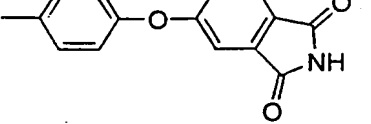
6				0.40	50% EtOAc / 50% hexane	460 (M+H)+ (HPLC ES-MS)	A3 C2d
7				0.79	50% EtOAc / 50% hexane	446 (M+H)+ (HPLC ES-MS)	A12 C2d

Table 3.

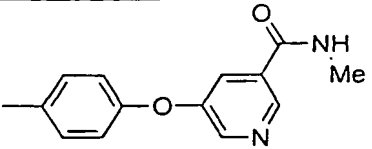
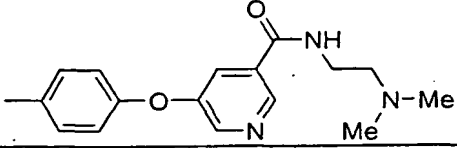
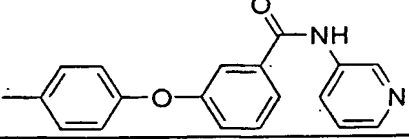
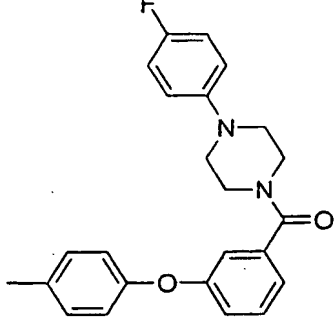
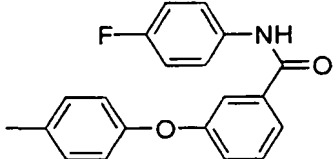
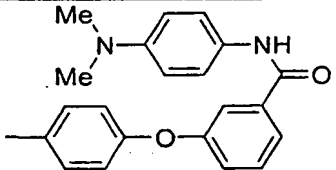
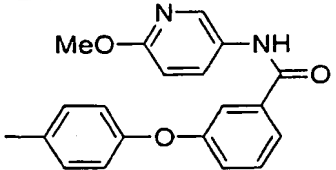
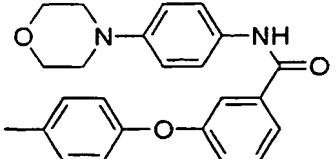
5-(Trifluoromethyl)-2-methoxyphenyl Ureas



Entry	R	mp (°C)	HPLC (min.)	TLC R _f	TLC Solvent System	Mass Spec. [Source]	Synth. Method
8		250 (dec)				460 (M+H)+ (FAB)	A13 C2a
9		206- 208		0.54	10% MeOH/ 90% CH ₂ Cl ₂	446 (M+H)+ (HPLC ES-MS)	A3 step 2, A8 step 4, B1, C1a
10				0.33	50% EtOAc/ 50% pet ether	445 (M+H)+ (HPLC ES-MS)	A13 C3
11				0.20	2% Et ₃ N/ 98% EtOAc	461 (M+H)+ (HPLC ES-MS)	A2 C4
12				0.27	1% Et ₃ N/ 99% EtOAc	447 (M+H)+ (HPLC ES-MS)	A2 C4
13				0.62	100% EtOAc	461 (M+H)+ (FAB)	A2 C2a
14		114- 117		0.40	1% Et ₃ N/ 99% EtOAc	447 (M+H)+ (FAB)	A2 C4

15		232-235		0.54	100% EtOAc	490 (M+H)+ (FAB)	A8 C2d
16		210-213		0.29	5% MeOH/ 45% EtOAc/ 50% pet ether	475 (M+H)+ (HPLC ES-MS)	A5 B1 C1c
17		187-188		0.17	50% EtOAc/ 50% pet ether	495 (M+H)+ (HPLC ES-MS)	A6 B1 C1a
18				0.48	100% EtOAc	475 (M+H)+ (HPLC ES-MS)	A2 step 4, B1 C1a
19		194-196		0.31	5% MeOH/ 45% EtOAc/ 50% pet ether	475 (M+H)+ (HPLC ES-MS)	A2 B1 C1a
20		214-216		0.25	5% MeOH/ 45% EtOAc/ 50% pet ether	495 (M+H)+ (HPLC ES-MS)	A2 C1a
21		208-210		0.30	50% EtOAc/ 50% hexane	481 (M+H)+ (HPLC ES-MS)	A19 C2a
22		188-190		0.30	70% EtOAc/ 50% hexane	447 (M+H)+ (HPLC ES-MS)	A15, step 4, C1a
23				0.50	70% EtOAc/ 30% hexane	472 (M+H)+ (FAB)	A3 B1 C1a

24		203-205		0.13	100% EtOAc	479 (M+H)+ (HPLC ES-MS)	A2 B1 C1a
25				0.09	75% EtOAc/ 25% hexane	458 (M+H)+ (HPLC ES-MS)	A12 C2d
26		169-171		0.67	50% EtOAc/ 50% pet ether	474 (M+H)+ (HPLC ES-MS)	A13 step 1, A13 step 4, A16, B1 C1a
27		218-219		0.40	50% EtOAc/ 50% pet ether	477 (M+H)+ (HPLC ES-MS)	A2 step 3b, A2 step 4, B1, C1a
28		212-214		0.30	40% EtOAc/ 60% hexane		A9 B1 C1a
29				0.33	50% EtOAc/ 50% pet ether	474 (M+H)+ (HPLC ES-MS)	A2 step 3b, A2 step 4, B1, C1a
30		210-211					A2 B1 C1a
31		210-204		0.43	10% MeOH/ CH2Cl2		A14 B1 C1a D4

32		247-249		0.57	10% MeOH/ CH ₂ Cl ₂		A14 B1 C1a D4
33		217-219		0.07	10% MeOH/ CH ₂ Cl ₂		A14 B1 C1a D4
34				0.11	70% EtOAc/ 30% hexane		A11 B1 C1f D1c
35				0.38	70% EtOAc/ 30% hexane		A11 B1 C1f D1c
36				0.77	70% EtOAc/ 30% hexane		A11 B1 C1f D1c
37				0.58	70% EtOAc/ 30% hexane		A11 B1 C1f D1c
38				0.58	70% EtOAc/ 30% hexane		A11 B1 C1f D1c
39				0.17	70% EtOAc/ 30% hexane		A11 B1 C1f D1c

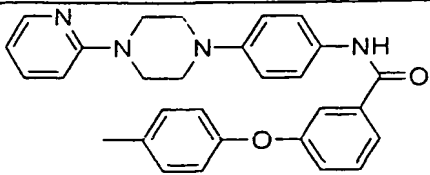
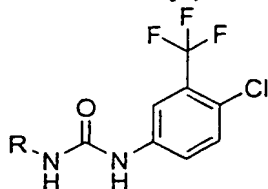
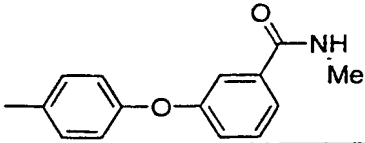
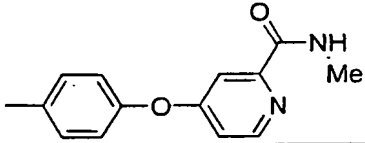
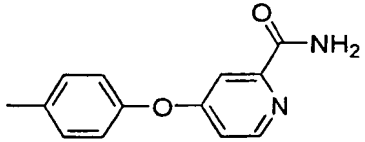
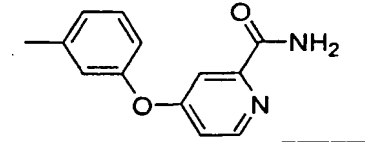
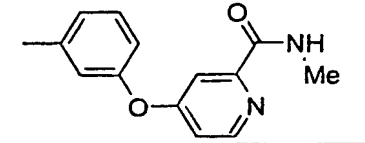
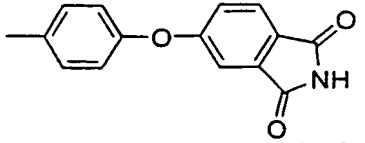
40				0.21	70% EtOAc/ 30% hexane		A11 B1 C1f D1c
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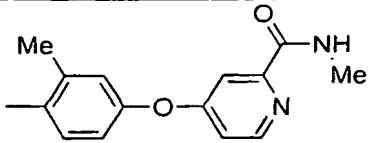
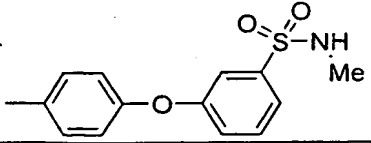
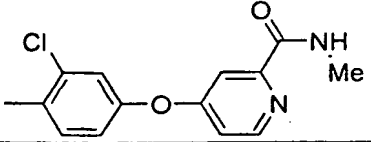
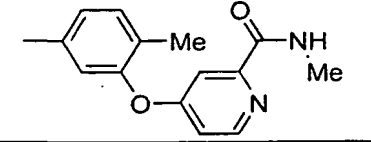
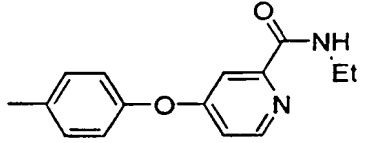
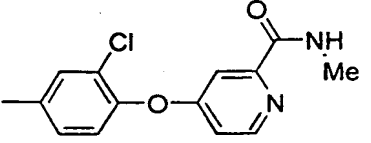
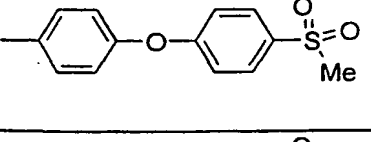
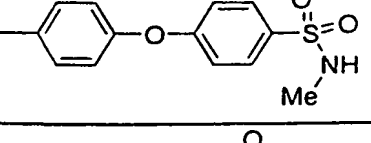
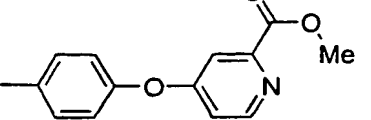
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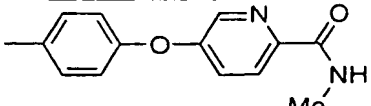
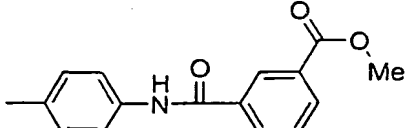
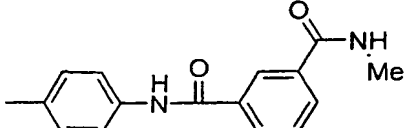
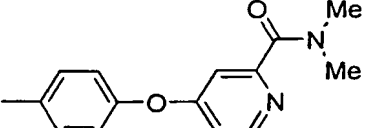
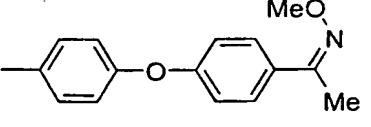
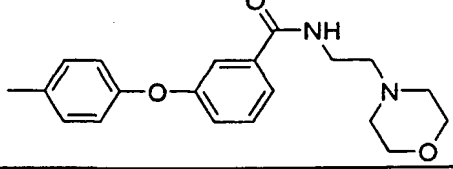
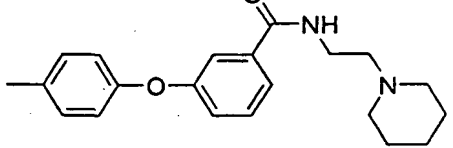
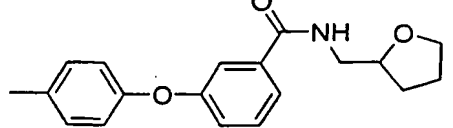
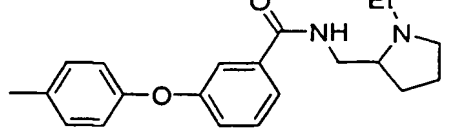
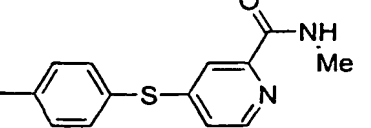
3-(Trifluoromethyl)-4-chlorophenyl Ureas

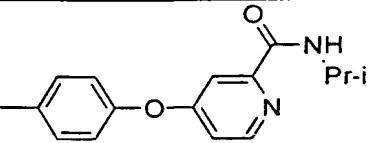
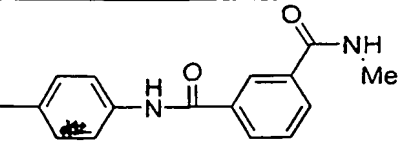
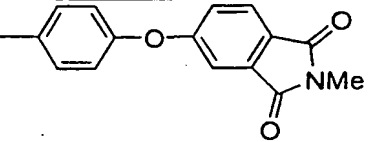
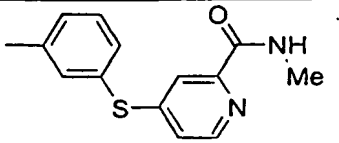
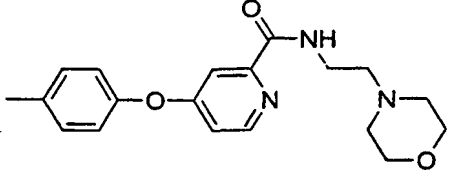
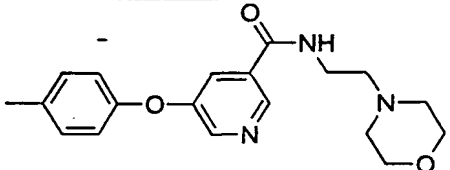
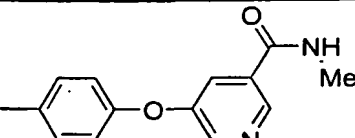
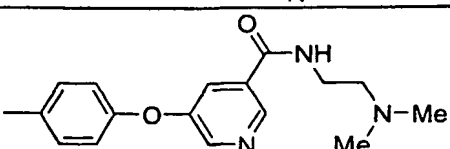
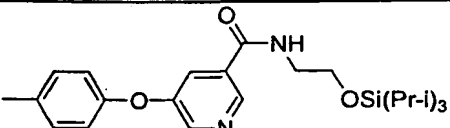


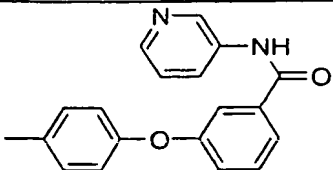
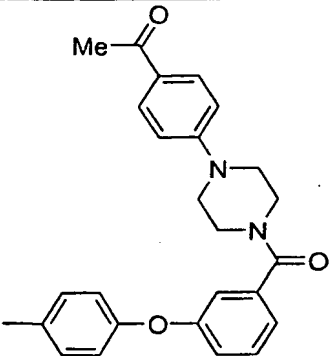
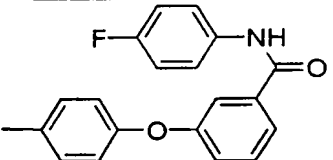
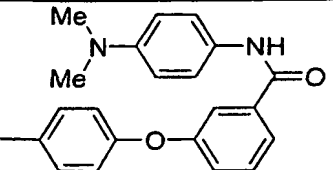
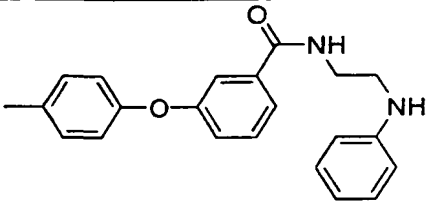
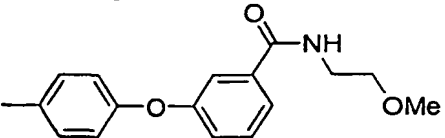
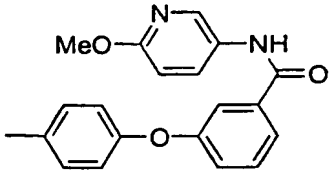
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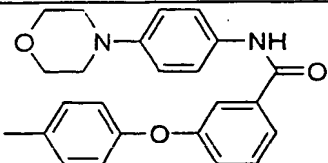
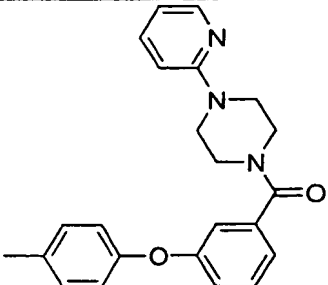
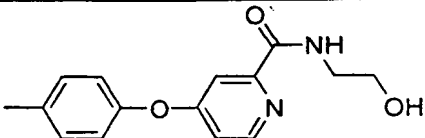
Entry	R	mp (°C)	HPLC (min.)	TLC R _f	TLC Solvent System	Mass Spec. [Source]	Synth. Method
41		163- 165		0.08	50% EtOAc/ 50% pet ether	464 (M+H)+ (HPLC ES-MS)	A13 C3
42		215		0.06	50% EtOAc/ 50% pet ether	465 (M+H)+ (HPLC ES-MS)	A2 C1a
43				0.10	50% EtOAc/ 50% pet ether	451 (M+H)+ (HPLC ES-MS)	A2 C1a
44				0.25	30% EtOAc/ 70% pet ether	451 (M+H)+ (HPLC ES-MS)	A2 C1a
45				0.31	30% EtOAc/ 70% pet ether	465 (M+H)+ (HPLC ES-MS)	A2 C1a
46		176- 179		0.23	40% EtOAc/ 60% hexane	476 (M+H)+ (FAB)	A3 C1a

47				0.29	5% MeOH/ 45% EtOAc/ 50% pet ether	478 (M+H)+ (HPLC ES-MS)	A5 C1c
48		206-209					A15 C1a
49		147-151		0.22	50% EtOAc/ 50% pet ether	499 (M+H)+ (HPLC ES-MS)	A6 C1a
50				0.54	100% EtOAc	479 (M+H)+ (HPLC ES-MS)	A2 C1a
51		187-189		0.33	5% MeOH/ 45% EtOAc/ 50% pet ether	479 (M+H)+ (HPLC ES-MS)	A2 C1a
52		219		0.18	5% MeOH/ 45% EtOAc/ 50% pet ether	499 (M+H)+ (HPLC ES-MS)	A2 C1a
53		246-248		0.30	50% EtOAc/ 50% hexane	485 (M+H)+ (HPLC ES-MS)	A19, C1a
54		196-200		0.30	70% EtOAc/ 30% hexane)	502 (M+H)+ (HPLC ES-MS)	A15 C1a
55		228-230		0.30	30% EtOAc/ 70% CH2Cl2	466 (M+H)+ (HPLC ES-MS)	

56		238-245					
57		221-222		0.75	80% EtOAc/ 20% hexane	492 (M+H)+ (FAB)	C1d D1a
58		247		0.35	100% EtOAc		C1d D1a D2
59		198-200		0.09	100% EtOAc	479 (M+H)+ (HPLC ES-MS)	A2 C1a
60		158-160		0.64	50% EtOAc/ 50% pet ether		
61		195-197		0.39	10% MeOH/ CH ₂ Cl ₂ 2		A13 C1a
62		170-172		0.52	10% MeOH/ CH ₂ Cl ₂ 2		A13 C1a
63		168-171		0.39	10% MeOH/ CH ₂ Cl ₂ 2		A13 C1a
64		176-177		0.35	10% MeOH/ CH ₂ Cl ₂ 2		A13 C1a
65		130-133				487 (M+H)+ (HPLC ES-MS)	A2 B1 C1a

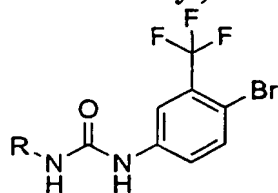
66		155					A2 C1a
67		225- 229		0.23	100% EtOAc		C1e D3 D1b
68		234- 236		0.29	40% EtOAc/ 60% hexane		A9 C1a
69				0.48	50% EtOAc/ 50% pet ether	481 (M+H)+ (HPLC ES-MS)	
70				0.46	5% MeOH/ 95% CH2Cl2	564 (M+H)+ (HPLC ES-MS)	A10 C1a
71		199- 201		0.50	10% MeOH/ CH2Cl 2		A14 C1a D4
72		235- 237		0.55	10% MeOH/ CH2Cl 2		A14 C1a D4
73		200- 201		0.21	50% MeOH/ CH2Cl 2		A14 C1a D4
74		145- 148					

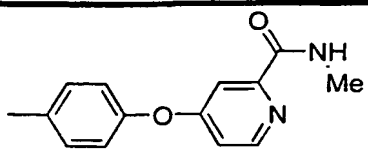
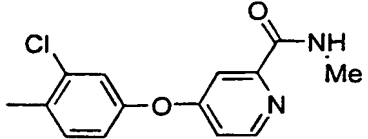
75				0.12	70% EtOAc/ 30% hexane	527 (M+H)+ (HPLC ES-MS)	A11 C1f D1c
76				0.18	70% EtOAc/ 30% hexane		A11 C1f D1c
77				0.74	70% EtOAc/ 30% hexane		A11 C1f D1c
78				0.58	70% EtOAc/ 30% hexane		A11 C1f D1c
79				0.47	70% EtOAc/ 30% hexane	569 (M+H)+ (HPLC ES-MS)	A11 C1f D1c
80				0.18	70% EtOAc/ 30% hexane	508 (M+H)+ (HPLC ES-MS)	A11 C1f D1c
81				0.58	70% EtOAc/ 30% hexane	557 (M+H)+ (HPLC ES-MS)	A11 C1f D1c

82				0.37	70% EtOAc/ 30% hexane	611 (M+H) ⁺ (HPLC ES-MS)	A11 C1f D1c
83				0.19	70% EtOAc/ 30% hexane		A11 C1f D1c
84		179- 183					A2 A17 C1a D5

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Table 5. 3-(Trifluoromethyl)-4-bromophenyl Ureas



Entry	R	mp (°C)	HPLC (min.)	TLC R _f	TLC Solvent System	Mass Spec. [Source]	Synth. Method
85		186- 187		0.13	50% EtOAc/ 50% pet ether	509 (M+H) ⁺ (HPLC ES-MS)	A2 B1 C1a
86		150- 152		0.31	50% EtOAc/ 50% pet ether	545 (M+H) ⁺ (HPLC ES-MS)	A6 B1 C1a

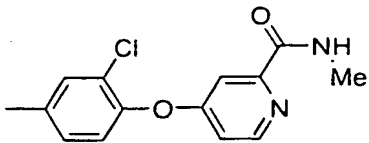
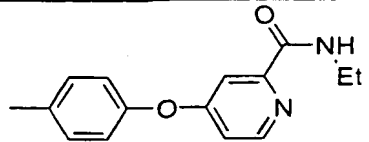
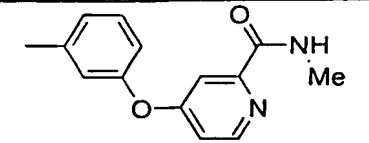
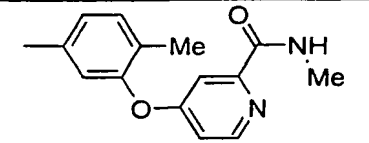
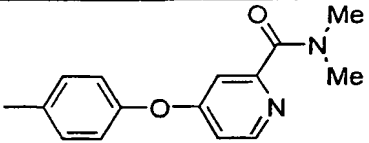
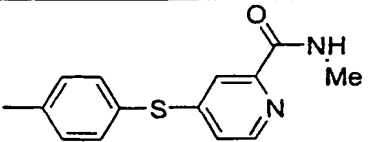
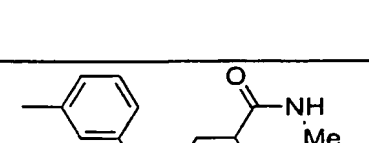
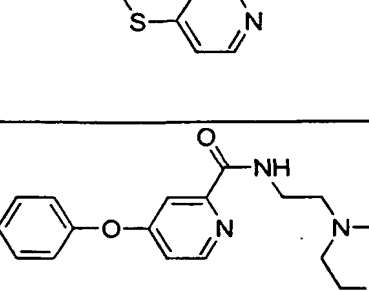
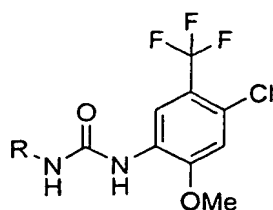
87		217-219		0.16	50% EtOAc/ 50% pet ether	545 (M+H)+ (HPLC ES-MS)	A2 B1 C1a
88		183-184		0.31	50% EtOAc/ 50% pet ether	525 (M+H)+ (HPLC ES-MS)	A2 B1 C1a
89				0.21	50% EtOAc/ 50% pet ether	511 (M+H)+ (HPLC ES-MS)	A2 B1 C1a
90				0.28	50% EtOAc/ 50% pet ether	525 (M+H)+ (HPLC ES-MS)	A2 B1 C1a
91		214-216		0.28	50% EtOAc/ 50% pet ether	522 (M+H)+ (HPLC ES-MS)	A2 B1 C1a
92				0.47	50% EtOAc/ 50% pet ether	527 (M+H)+ (HPLC ES-MS)	A2 step 3b, A2 step 4, B1, C1a
93				0.46	50% EtOAc/ 50% pet ether	527 (M+H)+ (HPLC ES-MS)	A2 step 3b, A2 step 4, B1, C1a
94		145-150		0.41	5% MeOH/ 95% CH2Cl2		A10 B1 C1a

Table 6.
Ureas

5-(Trifluoromethyl)-4-chloro-2-methoxyphenyl



Entry	R	mp (°C)	HPLC (min.)	TLC R _f	TLC Solvent System	Mass Spec. [Source]	Synth. Method
95		140- 144		0.29	5% MeOH/ 45% EtOAc/ 50% pet ether	495 (M+H)+ (HPLC ES-MS)	A2 A7 B1 C1a
96		244- 245		0.39	5% MeOH/ 45% EtOAc/ 50% pet ether	529 (M+H)+ (HPLC ES-MS)	A6 A7 B1 C1a
97		220- 221		0.25	5% MeOH/ 45% EtOAc/ 50% pet ether	529 (M+H)+ (HPLC ES-MS)	A2 A7 B1 C1a
98				0.27	5% MeOH/ 45% EtOAc/ 50% pet ether	495 (M+H)+ (HPLC ES-MS)	A2 A7 B1 C1a
99		180- 181		0.52	5% MeOH/ 45% EtOAc/ 50% pet ether	509 (M+H)+ (HPLC ES-MS)	A2 A7 B1 C1a

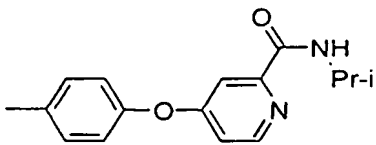
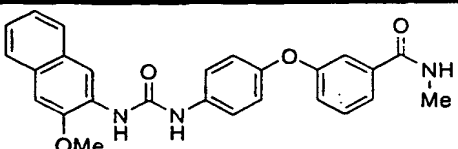
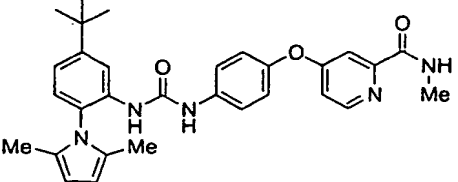
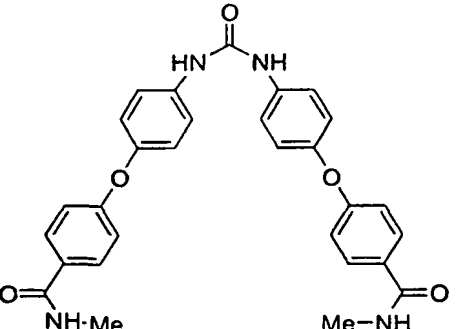
100		162-165					A2 A7 B1 C1a
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Table 7. Additional Ureas

Entry	R	mp (°C)	HPLC (min.)	TLC R _f	TLC Solvent System	Mass Spec. [Source]	Synth. Method
101		162- 165					A1 A2 C3
102				0.10	50% EtOAc/ 50% hexane	442 (M+H)+ (HPLC ES-MS)	A2 A4 C2d
103		125- 130		0.24	40% EtOAc/ 60% hexane	512 (M+H)+ (FAB)	A2 C2b

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BIOLOGICAL EXAMPLES

P38 Kinase Assay:

The *in vitro* inhibitory properties of compounds were determined using a p38 kinase inhibition assay. P38 activity was detected using an *in vitro* kinase assay
5 run in 96-well microtiter plates. Recombinant human p38 (0.5 µg/mL) was mixed with substrate (myelin basic protein, 5 µg/mL) in kinase buffer (25 mM Hepes, 20 mM MgCl₂ and 150 mM NaCl) and compound. One µCi/well of ³³P-labeled ATP (10 µM) was added to a final volume of 100 µL. The reaction was run at 32 °C for 30 min. and stopped with a 1M HCl solution. The amount of radioactivity
10 incorporated into the substrate was determined by trapping the labeled substrate onto negatively charged glass fiber filter paper using a 1% phosphoric acid solution and read with a scintillation counter. Negative controls include substrate plus ATP alone.

All compounds exemplified displayed p38 IC₅₀s of between 1 nM and 10
15 µM.

LPS Induced TNFα Production in Mice:

The *in vivo* inhibitory properties of selected compounds were determined using a murine LPS induced TNFα production *in vivo* model. BALB/c mice
20 (Charles River Breeding Laboratories; Kingston, NY) in groups of ten were treated with either vehicle or compound by the route noted. After one hour, endotoxin (*E. coli* lipopolysaccharide (LPS) 100 µg) was administered intraperitoneally (i.p.). After 90 min, animals were euthanized by carbon dioxide asphyxiation and plasma was obtained from individual animals by cardiac puncture into heparinized tubes.
25 The samples were clarified by centrifugation at 12,500 x g for 5 min at 4 °C. The supernatants were decanted to new tubes, which were stored as needed at -20 °C. TNFα levels in sera were measured using a commercial murine TNF ELISA kit (Genzyme).

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

- 5 From the foregoing discussion, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

D is $-\text{NH}-\text{C}(\text{O})-\text{NH}-$,

A is a substituted moiety of up to 40 carbon atoms of the formula: $-\text{L}-(\text{M}-\text{L}^1)_q$, where L is a 5 or 6 membered cyclic structure bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L^1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-\text{SO}_2\text{R}_x$, $-\text{C}(\text{O})\text{R}_x$ and $-\text{C}(\text{NR}_y)\text{R}_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which

optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$, with R^7 as defined above.

2. A method as in claim 1 for the treatment of a cancerous cell growth mediated by p38 kinase.

3. A method as in claim 1 for the treatment of a disease other than cancer.

4. A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, temporomandibular joint disease or demyelinating disease of the nervous system.

5. A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement.

6. A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is an infectious disease selected from

the group consisting of tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enterotoxin A resulting from *Staphylococcus* infection, meningococcal infection, and infections from *Borrelia burgdorferi*, *Treponema pallidum*, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

7. A method as in claim 1 wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined in claim 1.

8. A method as in claim 7, wherein said substituted cyclic moiety L¹ is phenyl, pyridyl or pyrimidinyl.

9. A method of claim 1 wherein L¹ is substituted by -C(O)R_x or -SO₂R_x, wherein R_x is NR_aR_b.

10. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L¹)_q, where L is a 6 membered aryl moiety or a 6 membered hetaryl moiety bound directly to D, L¹ comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L¹ contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷; and

wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-, CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined above.

11. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I :



or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L¹)_q, where L is a substituted or unsubstituted phenyl or pyridine moiety bound directly to D, L¹ comprises a substituted phenyl, pyridine or pyrimidinyl moiety, M is a bridging group having at least one atom, q is an integer of from 1-3; and

B is a substituted or unsubstituted phenyl or pyridine group bound directly to D,

wherein L¹ is substituted by at least one substituent selected from the group consisting of -SO₂R_x, -C(O)R_x and -C(NR_y)R_z,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-C(O)-$, a C_1 - C_5 divalent alkylene group or a substituted C_1 - C_5 divalent alkylene group bound to the moiety L to form a cyclic

structure with at least 5 members, wherein the substituents of the substituted C_1 - C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, CHX^a- , $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$; with R^7 is as defined above; and

wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-, -CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined above.

12. A method for the treatment of a disease mediated by p38 kinase other than cancer which comprises administering a compound selected from the group consisting of

the 3-*tert*-butyl phenyl ureas:

N-(3-*tert*-butylphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea

and

N-(3-*tert*-butylphenyl)-*N'*-(4-(4-acetylphenoxy)phenyl) urea;

the 5-*tert*-butyl-2-methoxyphenyl ureas:

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1,3-dioxoisindolin-5-yloxy)phenyl) urea,

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1-oxoisindolin-5-yloxy)phenyl)

urea,

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea and

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea;

the 2-methoxy-5-(trifluoromethyl)phenyl ureas:

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

the 4-chloro-3-(trifluoromethyl)phenyl ureas:

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea and

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

the 4-bromo-3-(trifluoromethyl)phenyl ureas:

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea,

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea; and

the 2-methoxy-4-chloro-5-(trifluoromethyl)phenyl ureas:

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea.

13. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising a compound of Formula I,



or a pharmaceutically acceptable salt thereof, in an amount effective to treat a disease mediated by p38 and a physiologically acceptable carrier:

wherein

D is $-\text{NH}-\text{C}(\text{O})-\text{NH}-$,

A is a substituted moiety of up to 40 carbon atoms of the formula: $-\text{L}-(\text{M}-\text{L}^1)_q$, where L is a 5 or 6 membered cyclic structure bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L^1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of $-CN$, $-CO_2R^7$, $-COR^7$, $-$

$C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$, with R^7 as defined above.

14. A pharmaceutical composition as in claim 13 wherein:

R_y is hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, C_{7-24} alkaryl, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having 0-3 heteroatoms selected from N, S and O, substituted C_6-C_{14} aryl, substituted C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C_{7-24} alkaryl or substituted C_7-C_{24} aralkyl, where R_y is a substituted group, it is substituted by halogen up to per halo,

R_z is hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatom, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_3-C_{12} hetaryl having 1-3 heteroatoms selected from, S, N and O, C_{7-24} alkaryl, C_{7-24} aralkyl, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_6-C_{14} aryl, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from S, N and O, substituted C_{3-12} hetaryl having 1-3 heteroatoms selected from N, O and S, substituted C_{7-24} alkaryl or substituted C_7-C_{24} aralkyl where R_z is a substituted group, it is substituted by halogen up to per halo, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl having 1-3 heteroatoms selected from N, S and O, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and $-C(O)R_g$.

R_a and R_b are,

a) independently hydrogen,

a carbon based moiety selected from the group consisting of C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_{3-12} hetaryl having 1-3 heteroatoms selected from O, N and S, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, C_7 - C_{24} alkaryl, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C_{6-12} aryl, substituted C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C_{7-24} aralkyl, substituted C_{7-24} alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6 - C_{12} halo substituted aryl up to per halo aryl, C_3 - C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3 - C_{12} hetaryl up to per halo heteraryl, halo substituted C_7 - C_{24} aralkyl up to per halo aralkyl, halo substituted C_7 - C_{24} alkaryl up to per halo alkaryl, and $-C(O)R_g$; or

$-OSi(R_f)_3$ where R_f is hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_3 - C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{6-12} aryl, C_3 - C_{12} hetaryl having 1-3 heteroatoms selected from O, S and N, C_{7-24} aralkyl, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_3 - C_{12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, substituted C_3 - C_{12} heteraryl having 1-3 heteroatoms selected from O, S, and N, substituted C_{6-12} aryl, and substituted C_{7-24} alkaryl, where R_f is a substituted group it is substituted halogen up to per halo, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 - C_{24} alkaryl, C_7 - C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6 - C_{12} halo substituted aryl up to per halo aryl, C_3 - C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3 - C_{12} hetaryl up to per halo heteraryl, halo substituted

C₇-C₂₄ aralkyl up to per halo aralkyl, halo substituted C₇-C₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g, or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O with substituents selected from the group consisting of halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇-C₂₄ alkaryl, C₇-C₂₄ aralkyl, halo substituted C₁₋₆ alkyl up to per halo alkyl, halo substituted C₆-C₁₂ aryl up to per halo aryl, halo substituted C₃-C₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃-C₁₂ hetaryl up to per halo heteraryl, halo substituted C₇-C₂₄ aralkyl up to per halo aralkyl, halo substituted C₇-C₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g, or

c) one of R_a or R_b is -C(O)-, a C₁-C₅ divalent alkylene group or a substituted C₁-C₅ divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C₁-C₅ divalent alkylene group are selected from the group consisting of halogen, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇-C₂₄ alkaryl, C₇-C₂₄ aralkyl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆-C₁₂ halo substituted aryl up to per halo aryl, C₃-C₁₂ halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃-C₁₂ hetaryl up to per halo heteraryl, halo substituted C₇-C₂₄ aralkyl up to per halo aralkyl, halo substituted C₇-C₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g,

where R_g is C₁₋₁₀ alkyl; -CN, -CO₂R_d, -OR_d, -SR_d, -NO₂, -C(O) R_e, -NR_dR_e, -NR_d C(O)OR_e and -NR_d C(O)R_e, and R_d and R_e are independently selected from the group consisting of hydrogen, C₁₋₁₀, alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, C₆₋₁₂ aryl, C₃-C₁₂ hetaryl with 1-3 heteroatoms selected from O, N and S and C₇-C₂₄ aralkyl, C₇-C₂₄ alkaryl, up to per halo substituted C₁-C₁₀ alkyl, up to per halo substituted C₃-C₁₀ cycloalkyl having 0-

3 heteroatoms selected from O, N and S, up to per halo substituted C_6-C_{14} aryl, up to per halo substituted C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and up to per halo substituted C_7-C_{24} aralkyl,

W is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C_1-C_{10} alkyl, substituted C_1-C_{10} alkoxy, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkenoyl, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C_6-C_{12} aryl, substituted C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, N and S, substituted C_7-C_{24} aralkyl, substituted C_7-C_{24} alkaryl, substituted C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and $-Q-Ar$;

R^7 is independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O,

N and S, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{14} alkaryl, C_7-C_{24} aralkyl, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_6-C_{14} aryl, up to per-halosubstituted C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_7-C_{24} aralkyl, up to per-halosubstituted C_7-C_{24} alkaryl, and up to per-halosubstituted C_4-C_{23} alkheteroaryl; and

each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₂-C₁₀ alkenyl, C₁-C₁₀ alkenoyl, C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, C₆-C₁₄ aryl, C₃-C₁₃ hetaryl having 1-3 heteroatoms selected from O, N and S, C₇-C₂₄ alkaryl, C₇-C₂₄ aralkyl, C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkoxy, substituted C₂-C₁₀ alkenyl, substituted C₁-C₁₀ alkenoyl, substituted C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C₆-C₁₂ aryl, substituted C₇-C₂₄ alkaryl, substituted C₇-C₂₄ aralkyl and substituted C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S; wherein if Z is a substituted group, the one or more substituents are selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷.

15. A pharmaceutical composition as in claim 13 wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined in claim 13.

16. A pharmaceutical composition as in claim 13 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by -OH.

17. A pharmaceutical composition as in claim 13 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by a moiety having an ionizable hydrogen and a pKa of 10 or less.

18. A pharmaceutical composition as in claim 13 wherein B of Formula I is a substituted or unsubstituted six member aryl moiety or six member hetaryl moiety, said hetaryl moiety having 1 to 4 members selected from the group of

hetaryl atoms consisting of nitrogen, oxygen and sulphur with the balance of the hetaryl moiety being carbon.

19. A pharmaceutical composition as in claim 13 wherein B of Formula I is an unsubstituted phenyl group, an unsubstituted pyridyl group, an unsubstituted pyrimidinyl group, a phenyl group substituted by a substituent selected from the group consisting of halogen and W_n wherein W and n are as defined in claim 13, a pyrimidinyl group substituted by a substituent selected from halogen and W_n, wherein W and n are as defined in Claim 13, or a pyridyl group substituted by a substituent selected from the group consisting of halogen and W_n wherein W and n are as defined in claim 13.

20. A pharmaceutical composition as in claim 13, wherein L, the six member cyclic structure bound directly to D, is a substituted or unsubstituted 6 member aryl moiety or a substituted or unsubstituted 6 member hetaryl moiety, wherein said hetaryl moiety has 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulphur with the balance of said hetaryl moiety being carbon, wherein the one or more substituents are selected from the group consisting of halogen and W_n, wherein W and n are as defined in claim 13.

21. A pharmaceutical composition as in claim 13, wherein L, the 6 member cyclic structure bound directly to D, is a substituted phenyl, unsubstituted phenyl, substituted pyridyl, unsubstituted pyridyl group, unsubstituted pyrimidinyl or substituted pyrimidinyl.

22. A pharmaceutical composition as in claim 13, wherein said substituted cyclic moiety L¹ comprises a 5 to 6 membered aryl moiety or hetaryl moiety, wherein said heteraryl moiety comprises 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulphur.

23. A pharmaceutical composition as in claim 13, wherein said substituted cyclic moiety L¹ is phenyl, pyridyl or pyrimidinyl and M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -

C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m- CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is hydrogen or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen up to pre halo.

24. A pharmaceutical composition as in claim 13 wherein L¹ is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C₁-C₁₀ alkyl, up to per halo substituted C₁-C₁₀ alkyl, -CN, -OH, halogen, C₁-C₁₀ alkoxy and up to per halo substituted C₁-C₁₀ alkoxy.

25. A pharmaceutical composition as in claim 13 wherein L¹ is substituted by -C(O)R_x.

26. A pharmaceutical composition as in claim 13 wherein L¹ is substituted by -C(O)R_x or -SO₂R_x, wherein R_x is NR_aR_b.

27. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising a compound of Formula I:



or a pharmaceutically acceptable salt thereof, in an amount effective to treat a disease mediated by p38 and a physiologically acceptable carrier, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L¹)_q, where L is a 6 membered aryl moiety or a 6 membered hetaryl moiety bound directly to D, L¹ comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L¹ contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound

directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen,

hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

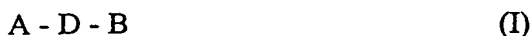
wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of $-CN$, -

CO_2R^7 , $-\text{C}(\text{O})\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{NO}_2$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents are selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{COR}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NO}_2$, $-\text{NR}^7\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, and $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$ with R^7 as defined above; and

wherein M is one or more bridging groups selected from the group consisting of $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^7)-$, $-(\text{CH}_2)_m-$, $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-(\text{CH}_2)_m\text{O}-$, $-(\text{CH}_2)_m\text{S}-$, $-(\text{CH}_2)_m\text{N}(\text{R}^7)-$, $-\text{O}(\text{CH}_2)_m-$, $-\text{CHX}^a-$, $-\text{CX}^a_2-$, $-\text{S}-(\text{CH}_2)_m-$ and $-\text{N}(\text{R}^7)(\text{CH}_2)_m-$, where $m = 1-3$, X^a is halogen and R^7 is as defined above.

28. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising a compound of Formula I:



or a pharmaceutically acceptable salt thereof, in an amount effective to treat a disease mediated by p38 and a physiologically acceptable carrier, wherein

D is $-\text{NH}-\text{C}(\text{O})-\text{NH}-$,

A is a substituted moiety of up to 40 carbon atoms of the formula: $-\text{L}-(\text{M}-\text{L}^1)_q$, where L is a substituted or unsubstituted phenyl or pyridyl moiety bound directly to D, L^1 comprises a substituted phenyl, pyridyl or pyrimidinyl moiety, M is a bridging group having at least one atom, q is an integer of from 1-3; and

B is a substituted or unsubstituted phenyl or pyridine group bound directly to D,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-\text{SO}_2\text{R}_x$, $-\text{C}(\text{O})\text{R}_x$ and $-\text{C}(\text{NR}_y)\text{R}_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo, and ;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy,

and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L¹ is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R⁷, -C(O)-R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NR⁷R⁷, -NO₂, -NR⁷C(O)R⁷, -NR⁷C(O)OR⁷ and halogen up to per-halo; with each R⁷ independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-, CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷ with R⁷ as defined above; and

wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m- CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined above.

29. A pharmaceutical composition as in claim 27 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by-OH.

30. A pharmaceutical composition as in claim 27, wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by a moiety having an ionizable hydrogen and a pKa of 10 or less.

31. A pharmaceutical composition as in claim 28, wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by-OH.

32. A pharmaceutical composition as in claim 28 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by a moiety having an ionizable hydrogen and a pKa of 10 or less.

33. A pharmaceutical composition as in claim 27 wherein L¹ is substituted by C(O)R_x or SO₂R_x, wherein R_x is NR_aR_b.

34. A pharmaceutical composition as in claim 28 wherein L¹ is substituted by C(O)R_x or SO₂R_x, wherein R_x is NR_aR_b.

35. A pharmaceutical composition as in claim 13 which comprises a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-

napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

36. A pharmaceutical composition as in claim 27 which comprises a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

37. A pharmaceutical composition as in claim 28 which comprises a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-

napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

38. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising a compound selected from the group consisting of the 3-*tert* butyl phenyl ureas:

N-(3-*tert*-butylphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea
and

N-(3-*tert*-butylphenyl)-*N'*-(4-(4-acetylphenoxy)phenyl) urea;

the 5-*tert*-butyl-2-methoxyphenyl ureas:

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1,3-dioxoisindolin-5-yloxy)phenyl) urea,

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1-oxoisindolin-5-yloxy)phenyl) urea,

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea and

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea;

the 2-methoxy-5-trifluoromethylphenyl ureas:

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

the 4-chloro-3-(trifluoromethyl)phenyl ureas:

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea and
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

the 4-bromo-3-(trifluoromethyl)phenyl ureas:

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea,
N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea; and

the 2-methoxy-4-chloro-5-(trifluoromethyl)phenyl ureas:

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/00768

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/535, 31/50, 31/445, 31/44, 31/40, 31/34, 31/17
US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/235.5, 237.2, 252.13, 253.01, 331, 345, 350, 416, 417, 428, 471, 596, 597, 598

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/33458 A1 (SMITHKLINE BEECHAM CORPORATION) 14 December 1995 (14.12.95), see pages 1-11 and the claims.	1-38



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X

document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y

document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z

document member of the same patent family

Date of the actual completion of the international search

25 MARCH 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/235.5, 237.2, 252.13, 253.01, 331, 345, 350, 416, 417, 428, 471, 596, 597, 598

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

STN (REGISTRY (CHEMICAL STRUCTURE SEARCH), CAPLUS, USPATFUL)

search terms: cancer, tumor, neoplasm, antineoplastic, anticancer, arthritis, inflammation, antiinflammatory, mmp, infection, autoimmune